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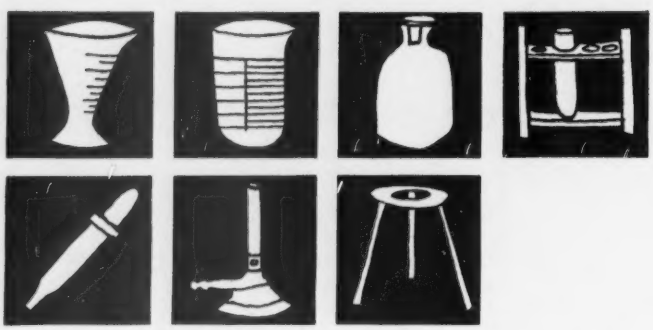

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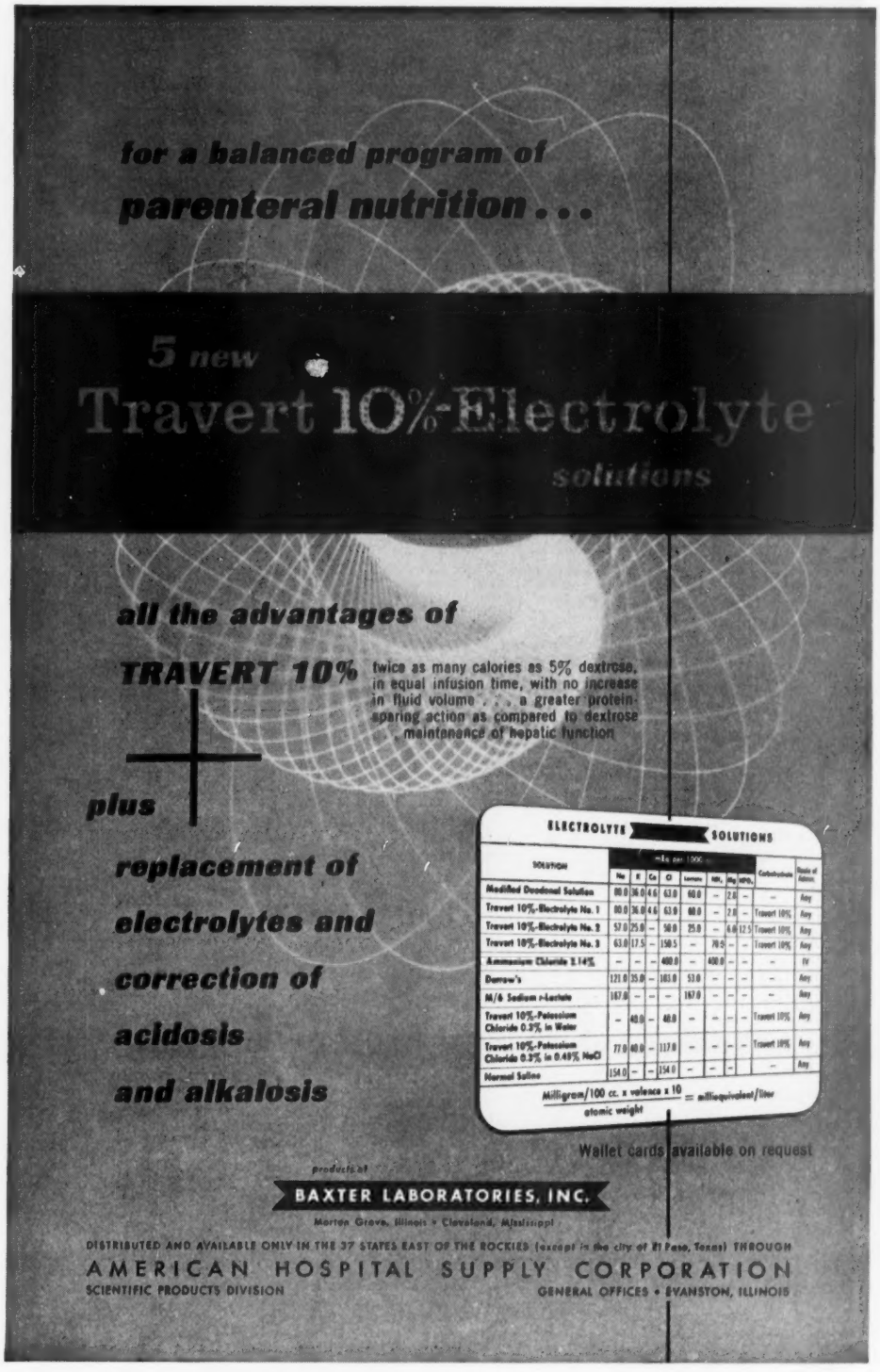
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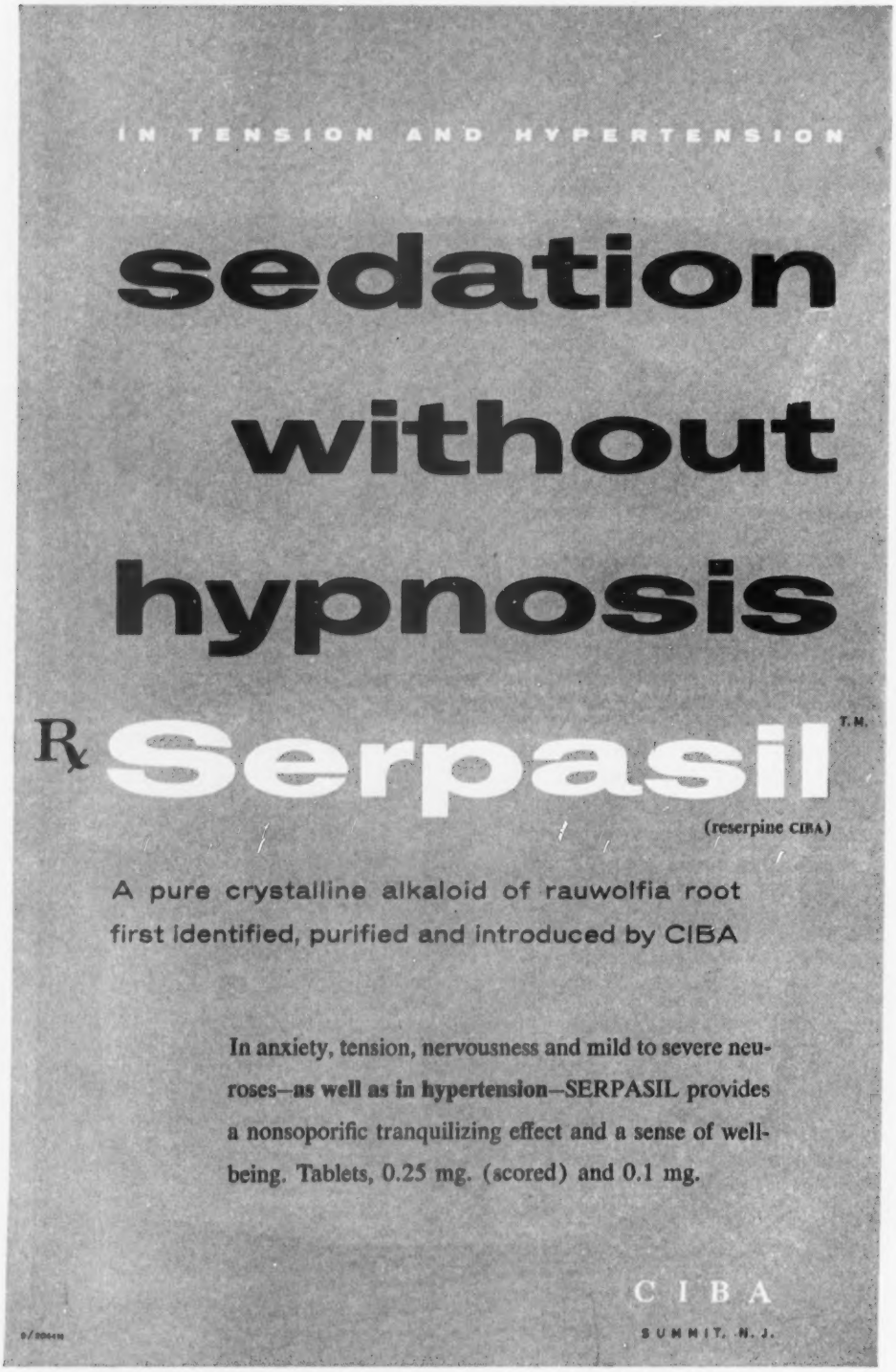
1. Welsh, A. L. and Ede, M.: A.M.A. Archives Derm. & Syph., June 1954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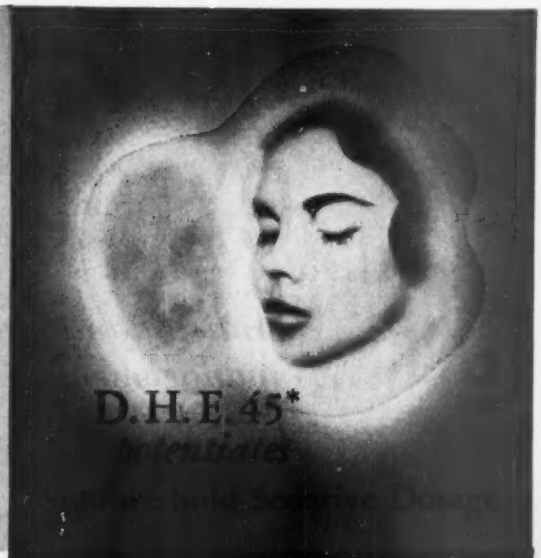

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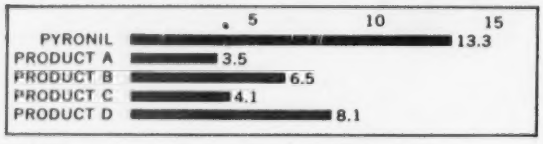

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Volume 251 AUGUST 5, 1954 Number 6

BRONCHOGENIC CARCINOMA*

A Study of 517 Cases

ADRIAN EHLER, M.D.,† ALLAN STRANAHAN, M.D.,‡ AND KENNETH B. OLSON, M.D.§

ALBANY, NEW YORK

VIRTUALLY all reports indicate a considerable rise in the incidence of bronchogenic carcinoma in white males.[1-4] The increase is less striking in females and less conclusive for races other than Caucasian. The histologic[5] and biologic characteristics of these tumors are probably more important in prognosis than early diagnosis. Many of the more malignant tumors are first discovered or made manifest through their metastasis and present hopeless problems at the time of diagnosis. Still other tumors may remain localized for long periods, producing chronic symptoms that are frequently misdiagnosed as asthma, cardiac disease, tuberculosis or chronic bronchitis. The last group of tumors offers the best opportunities for surgical cure. A small percentage of these patients in nearly every clinic have survived for five years or more, and it seems likely that with more prompt recognition and with better methods of arousing suspicion of cancer (such as cytologic examination of sputum) more of the biologically favorable cases can be salvaged.

Some of the larger thoracic-surgery clinics[2,5] have indicated that more than fifty per cent of patients with bronchogenic carcinoma are explored when first seen and that perhaps half these cases are suitable for resection. It is our impression that these figures are somewhat at variance with our experience and perhaps indicate that many patients with obvious metastasis or in too poor condition for surgery were never sent to special clinics for thoracic-surgery evaluation. The Albany Hospital is a general hospital of 700 beds. It serves as a diagnostic and treatment center for a moderate-sized metropolitan area and a large rural area. Because of this it is believed that our figures may be more representative of the over-all problem of bronchogenic cancer and more in agreement with those presented by Lindskog[6] and Bloomer.[7] Since 1940 there has been an active thoracic-surgery service at the Albany Hospital, and the following report includes all cases of bronchogenic cancer examined on this service as well as those diagnosed on other services. It is believed that the diagnostic methods and the criteria for exploration and resection are similar to those in general use. Virtually no palliative resections were done in the presence of proved distant metastasis, and unfortunately, in many cases, the diagnosis was not made until metastasis had occurred.

MATERIAL

In the seventeen years from 1936 to 1951, inclusive, 517 cases of bronchogenic cancer were admitted to the Albany Hospital. Table 1 gives a résumé of the histologic types of cancer, with an indication of the incidence. There were 103 cases in which no pathological diagnosis was available. In these cases the clinical and x-ray impression was bronchogenic carcinoma. Undoubtedly, there were inaccuracies in diagnosis in this group, but it would be more inaccurate to exclude them. There were 57 cases in which the histologic type was unclassified. In these cases either the diagnosis was made by cytologic examination of sputum or bronchial secretion or the biopsy did not permit a more definitive diagnosis. Four cases of bron-

TABLE 1. *Classification of Bronchogenic Carcinomas According to Cell Type.*

CELL TYPE	NO. OF CASES
No pathological diagnosis	103 (19.9%)
Squamous cell	172 (33.2%)
Anaplastic	147 (28.4%)
Unclassified	57 (11.1%)
Adenocarcinoma	34 (6.6%)
Bronchiolar	4 (0.8%)
Total	517

*From the Department of Surgery, Thoracic Surgery Service and the Department of Medicine, Subdepartment of Oncology, Albany Medical College.

Aided by a grant from the New York State Department of Health, Cancer Control Division, Paul Gerhardt, M.D., director.

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‡Assistant professor of surgery, Albany Medical College; attending thoracic surgeon, Albany Hospital.

§Assistant professor of medicine and director, Division of Oncology, Department of Medicine, Albany Medical College; attending physician in oncology, Albany Hospital.

chiolar or alveolar-cell carcinoma are included for the sake of completeness but are excluded from the remainder of the discussion since they were considered to represent a different pathologic entity from the usual types of pulmonary cancer. The commonest type

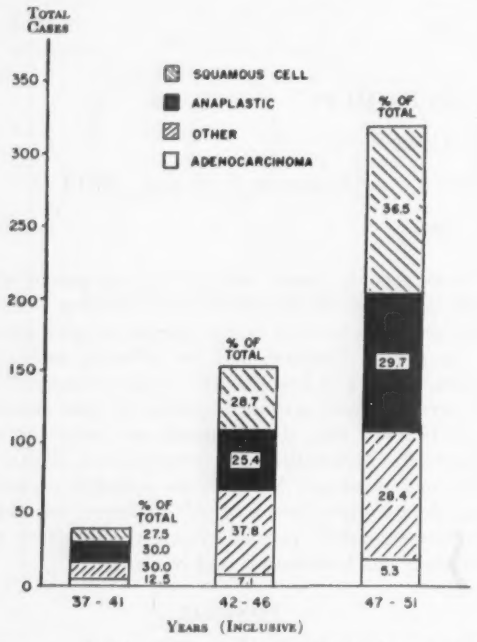

FIGURE 1. *Incidence of Bronchogenic Carcinoma at the Albany Hospital by Five-Year Periods from 1937 through 1951.*

Four cases of bronchiolar carcinoma have been excluded.

of cancer was squamous cell, and nearly as numerous were anaplastic carcinomas, which some[3] believe to be a variant of squamous-cell carcinoma and which in this study included the large-cell as well as the oat-cell or small-cell tumors. Together, these two types comprised 61.6 per cent of all carcinomas and 90.4 per cent of 353 tumors classified according to cell type. All adenomas have been excluded.

INCIDENCE

Figure 1 graphically portrays the incidence of bronchogenic carcinoma through three five-year periods from 1937 to 1951, inclusive. Four cases before 1937 are excluded. In the last five years there have been 320 cases as compared with 40 cases between 1937 and 1941 inclusive—an increase of 700 per cent. The rise in incidence has been chiefly in squamous-cell carcinoma although all types have increased. Adenocarcinoma is more frequent but has steadily declined, from 12.5 per cent of the total in the first period to 5.3 per cent of the total in the last period. This is in general agreement with experience reported elsewhere.[3]

SEX INCIDENCE

Table 2 presents the sex incidence. It is striking that the high incidence of males prevails chiefly in the squamous-cell and anaplastic types of cancer. The ratio of males to females in the group with adenocarcinoma is only 2.7:1.

AGE INCIDENCE

The age incidence according to cell type is given in Table 3. In 59.8 per cent of anaplastic cancers and 70.6 per cent of adenocarcinoma the diagnosis was made before the age of sixty. In all other groups more than half the tumors were discovered after the age of sixty. There were 13 patients below the age of forty, and 3 over the age of eighty. The youngest was twenty-eight, and the oldest eighty-four. Seventy-three and nine tenths per cent of all patients were in the fifth and sixth decades. This is in agreement with other large series.[8]

SYMPTOMS

Symptoms of bronchogenic carcinoma have been divided into two groups according to their probable cause. Thus, hemoptysis, cough and wheezing represent symptoms of bronchial erosion, irritation or narrowing. Other symptoms, such as pain, hoarseness, cerebral symptoms and dysphagia, are believed to indicate fairly conclusively that the cancer has spread

TABLE 2. *Cases of Bronchogenic Carcinoma According to Sex and Race for Each Cell Type.*

SEX	RACE	TOTALS		NO PATHOLOGICAL DIAGNOSIS		SQUAMOUS CELL		ANAPLASTIC		UNCLASSIFIED		ADENOCARCINOMA	
		NO.	PERCENTAGE	NO.	PERCENTAGE	NO.	PERCENTAGE	NO.	PERCENTAGE	NO.	PERCENTAGE	NO.	PERCENTAGE
Male		477	93.0	97	94.2	165	95.9	140	95.2	50	87.7	25	73.5
	White	468	91.2	97	94.2	163	94.8	135	91.8	48	84.2	25	73.5
	Negro	8	1.6	—	—	2	1.1	4	2.7	2	3.5	—	—
	Mongolian	1	0.2	—	—	—	—	1	0.7	—	—	—	—
Female	white	36	7.0	6	5.8	7	4.1	7	4.8	7	12.3	9	26.5
Totals		513	100.0	103	100.0	172	100.0	147	100.0	57	100.0	34	100.0
Ratio of males to females		13.2		16.1		23.5		20.0		7.1		2.7	

beyond the lung. Still others, such as weight loss, fever, fatigue and dyspnea, are more difficult to classify but again most likely represent an advanced state of disease. Table 4 presents the initial symptom according to type of tumor; it is of interest that two thirds of squamous-cell carcinomas begin with bronchial symptoms whereas only 44.1 per cent of adenocarcinomas have a similar onset. Nearly half the anaplastic carcinomas are first manifested by extrabronchial symptoms. These figures suggest that anaplastic lesions and adenocarcinomas have a greater tendency to spread beyond the confines of the lung before bronchial erosion occurs than squamous-cell carcinoma does. Table 5 gives the incidence of symptoms in all cases. The first three symptoms in the order of their development have been tabulated at the time of diagnosis. Cough with expectoration was present in nearly two thirds of patients by the time a diagnosis was established. The high incidence of cerebral symptoms (10.9 per cent) at the time of diagnosis may have been due to the presence of an active neurosurgical service at the Albany Hospital. Many of these patients were referred because it was believed that a primary brain tumor existed.

TABLE 3. *Distribution of Bronchogenic Carcinoma According to Age and Cell Type.*

AGE	NO. OF PATIENTS	PERCENTAGE	NO PATHOLOGICAL DIAGNOSIS	INCIDENCE OF SQUAMOUS-CELL TYPE	INCIDENCE OF ANAPLASTIC TYPE	INCIDENCE OF UNCLASSIFIED TYPE	INCIDENCE OF ADENOCARCINOMAS
yr.			%	%	%	%	%
Under 40	13	2.5	1.9	0.6	4.1	1.8	8.8
40–49	64	12.5	13.6	11.6	12.2	12.3	14.7
50–59	186	36.3	23.3	37.2	43.5	31.5	47.1
60–69	193	37.6	40.8	39.5	35.4	40.3	23.5
70–79	50	9.7	18.4	10.5	3.4	10.5	5.9
80 and over	3	0.6	1.0	—	0.7	1.8	—
Unknown	4	0.8	1.0	0.6	0.7	1.8	—

TABLE 4. *Initial Symptom in Each Cell Type of Bronchogenic Carcinoma.*

INITIAL SYMPTOM	ALL CASES	NO PATHOLOGICAL DIAGNOSIS NO. OF CASES	SQUAMOUS-CELL CARCINOMA NO. OF CASES	ANAPLASTIC CARCINOMA NO. OF CASES	UNCLASSIFIED NO. OF CASES	ADENOCARCINOMA NO. OF CASES
Bronchial:						
Cough, with expectoration	205	39	77	57	21	11
Cough, dry	42	10	13	14	3	2
Blood-streaked sputum	20	2	10	4	3	1
Hemoptysis	13	—	7	4	1	1
None	8	1	5	2	—	—
Wheezing	8	—	3	4	1	—
Totals	296(57.7%)	52(50.4%)	115(66.7%)	85(57.8%)	29(50.8%)	15(44.1%)
Extrabronchial:						
Pain, thoracic	58	13	18	17	10	—
Pain, other	44	10	8	15	6	5
Dyspnea	37	11	8	9	6	3
Fatigue	24	3	7	7	2	5
Cerebral	13	5	2	1	1	4
Weight loss	9	6	2	—	—	1
Fever	5	—	3	2	—	—
Palpable mass	6	1	2	1	2	—
Hoarseness	4	—	2	2	—	—
Dysphagia	1	—	1	—	—	—
Other	15	1	4	8	1	1
Unknown	1	1	—	—	—	—
Totals	217(42.3%)	51(49.5%)	57(33.2%)	62(42.2%)	28(49.2%)	19(55.9%)

Primary Site

Figure 2 indicates the location of the primary site of carcinoma in 513 cases. The tumors were localized by either radiologic or surgical findings. It was not possible to localize the primary site in nearly 10 per cent of cases. In the remaining cases 52.3 per cent were in the right, and 37.7 per cent in the left lung. Both upper lobes accounted for 53.7 per cent of all tumors, or well over half the 90 per cent that could be localized. Fifty-seven and five-tenths per cent of squamous-cell carcinomas were in the upper lobes whereas 47.5 per cent of the anaplastic type and only 44.0 per cent of the adenocarcinomas were in this position. The commonest single location of all tumors was in the right upper lobe. Adenocarcinomas tended to be more evenly distributed throughout the lungs than either of the other two cell types.

Table 5. *Symptoms in 513 Cases of Bronchogenic Carcinoma in Order of Frequency at Time of Diagnosis.*

Symptom	No. of Cases	Percentage
Cough, expectoration	318	62.0
Pain, thoracic	208	40.5
Dyspnea	156	30.4
Blood-streaked sputum	142	27.7
Pain, extrathoracic	93	18.1
Fatigue	90	17.5
Wheezing	75	14.6
Cough, dry	60	11.7
Fever	59	11.5
Cerebral	56	10.9
Hemoptysis	52	10.1
Weight loss	49	10.0
Hoarseness	40	7.8
Palpable mass	26	5.1
Dysphagia	18	3.5
Others	65	12.7

Size of Tumor

Roentgenograms of patients at the time of diagnosis were studied in an effort to delineate and measure the primary tumor mass. In thirty-two and five-tenths per cent of patients a round or measurable tumor mass could be observed. Approximately two thirds of measurable tumor masses were from 2 to 8 cm. in diameter, and the remaining third were 9 cm. or over. This proportion was fairly constant for all cell types. There was no striking preponderance of any one cell type in peripheral or measurable tumors. More anaplastic carcinomas were measurable than any other cell type (40.8 per cent), and the least number of measurable tumors were in the squamous-cell group (24.4 per cent) and unclassified carcinomas (24.6 per cent). This difference has some statistical significance, but when it is realized that an abscess or localized fluid collection can often present a measurable mass these figures are of dubious clinical significance. The figures do serve to emphasize that most lung tumors of the primary type are first indicated by nonspecific signs such as atelectasis, pneumonitis, lung abscess and areas of infiltration rather than by circumscribed or measurable tumor masses.

Operative Status and Treatment

The status of these cases at the time of diagnosis is presented in Table 6. The term "operable" refers to the clinical opinion that there was no evidence of spread beyond the thorax and that operation was indicated to determine the "resectability" of the lesion. In no cell type was "operability" present in half or more of the cases; 40.1 per cent of squamous-cell and 29.9 per cent of anaplastic-cell carcinomas were considered operable at diagnosis. The lowest percentages of "operability" were in the unclassified carcinomas and in those with no pathological diagnosis. Patients in the last two groups were frequently too ill or too cachectic for further diagnostic or possibly curative procedures. Of the entire group 30 per cent were considered operable. Most of the remaining 70 per cent (359 cases) were considered inoperable because of metastasis (87.4 per cent) or because the general condition of the patient was so poor that an operation was not advisable (16.4 per cent).

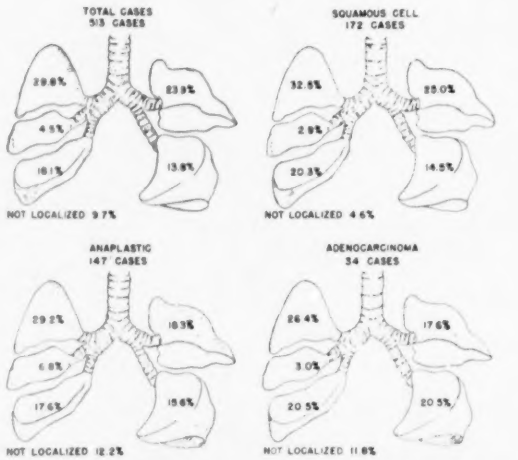

Figure 2. *Location of the Primary Tumor According to Lobe Affected.*

Localization was made by examination of the chest roentgenogram or at operation.

Metastases were regarded as a contraindication to surgical treatment when they were present at distant sites or were so extensive locally that it was not deemed advisable to attempt resection. There were a number of patients in extremely poor general condition with

evidence of metastasis. Eight patients, or 2.1 per cent, of the total not operated on were considered to be operable and refused operation.

Of the 146 patients (Table 6) operated on the highest incidence of resections occurred in the group

Results

Follow-up data for one year have been obtained for the entire series and for 220 patients operated on five years or more before the close of this study. Most

Table 6. *Operative Experience in Bronchogenic Carcinoma According to Cell Type.*

Status	Totals	No Pathological Diagnosis no. of cases	Squamous-Cell Carcinoma no. of cases	Anaplastic Carcinoma no. of cases	Unclassified no. of cases	Adenocarcinomas no. of cases
Not operable	359	85	103	103	46	22
Operable*	154(30.0%)	18(17.5%)	69(40.1%)	44(29.9%)	11(19.3%)	12(35.3%)
Totals	513	103	172	147	57	34
Operation:						
Exploration only	87	12	32	27	10	6
Pneumonectomy	45	—	29	12	—	4
Lobectomy	12	—	5	5	—	2
Wedge resection	2	—	1	—	1	—
Totals	146	12	67	44	11	12
Resection	59(40.4%†)	0.0	35(52.2%†)	17(38.8%†)	1(9.0%†)	6(50.0%†)

*8 patients refused operation.
†Computed according to patients operated on.

of squamous-cell carcinomas (52.2 per cent) and in the adenocarcinomas (50.0 per cent); 38.8 per cent of anaplastic carcinomas explored were resected. As might have been expected, there were virtually no resections in the groups with no pathological diagnosis or in which the cell type could not be classified. The immediate operative results are shown in Table 7. Operative mortality has been arbitrarily defined as all deaths that occurred within thirty days of operation. There were 12 lobectomies, with no operative mortality. There were 45 pneumonectomies, with 8 deaths, or an operative mortality of 17.8 per cent, and it is of interest that the operative mortality decreased to 7.1 per cent in the last two years of this study. The operative mortality of thoracic exploration has decreased from 25 per cent to 7.7 per cent during the last ten years. There were 11 deaths among 87 cases within thirty days of thoracic exploration. It is known that 5 of these deaths (5.7 per cent of thoracic explorations) were definitely postoperative and due to hemorrhage, bronchopleural fistula or empyema. Six additional deaths occurred within thirty days of thoracic exploration but after discharge from the hospital, and the exact cause of death in these cases is not known. It is possible that in some of the postoperative deaths tumor metastasis was hastened by operation.

living patients were examined, but examination was not possible in some and it is quite probable that many of the survivors have persistent disease. In patients who died elsewhere than at the Albany Hospital dates and causes of death were obtained from the death certificate. Table 8 gives the survival rate of patients after a resection and those either explored or not operated on. Seventy-nine of 513 patients, or 15.4 per cent, survived for one year or more after diagnosis. Forty-eight of 454, or 10.6 per cent, survived for one year or more without pulmonary resection, and 31 of 59, or 52.5 per cent survived for at least one year after some type of pulmonary resection. There were 5 who survived for five years, or 2.3 per cent of the total

Table 7. *Operative Mortality According to Type of Operation.*

Years Inclusive	Total Cases	Total Operations	Total Postoperative Deaths*		No. of Lobectomies	Deaths after Lobectomy*	No. of Pneumonectomies	Deaths after Pneumonectomy*		No. of Exploratory Operations	Deaths after Exploration*	
1935–40	31	—	—	(—)	—	—	—	—	—	—	—	—
1941–43	52	10	4	(40.0%)	—	—	2	2	(100.0%)	8	2	(25.0%)
1944–46	115	23	4	(17.4%)	1	—	6	1	(16.7%)	16	3	(18.8%)
1947–49	166	64	8	(12.5%)	4	—	23	4	(17.4%)	37	4	(10.8%)
1950–51	149	47	3	(6.4%)	7	—	14	1	(7.1%)	26	2	(7.7%)
Totals	513	144	19	(13.2%)	12	—	45	8	(17.8%)	87	11	(12.6%)

*Includes all deaths within 30 days of operation.

of 220 cases followed for five years; some type of pulmonary resection was done in 4 of these. Two of these patients had adenocarcinomas, and 2 had squamous-cell carcinomas. An additional patient with squamous-cell carcinoma survived for five years from the date of diagnosis by biopsy without surgery. One of 4 patients with lobectomy has survived for five years, and 3 of 20 with pneumonectomy have survived for five years. There were no five-year survivals in any group except squamous-cell lesions and adenocarcinomas. It is of interest that in 24 cases resected over five years ago, 4 patients, or 16.7 per cent of

the total, were alive at the time this study was completed. If the postoperative deaths are excluded, 4 of 19 patients with resections, or 21.1 per cent, survived for five years.

Figure 3 indicates the probability of survival for 56 white males in whom some type of resection was performed and in 415 white males in whom no resection could be performed. Less than 5 per cent of patients cases have been studied according to lymph-node involvement at the time of operation. Sixty-five and five-tenths per cent of squamous-cell carcinomas, 42.8 per cent of anaplastic tumors and 66 per cent of adenocarcinomas were without known lymph-node involvement at the time of resection. The survival rate at the end of one year was the same regardless of metastasis. Of the patients who survived operation

TABLE 8. *Survival after Diagnosis in Patients with Bronchogenic Carcinoma (Resectable and Nonresectable Cases).*

Type of Tumor	Patients with No Resection Followed for 1 Yr.			Patients with Resection Followed for 1 Yr.			Patients with No Resection Followed for 5 Yr.*			Patients with Resection Followed for 5 Yr.*		
	Totals	Survivals		Totals	Survivals		Totals	Survivals		Totals	Survivals	
No pathological diagnosis	103	15	(14.6%)	—	—	(—)	53	—	(—)	—	—	(—)
Squamous cell	137	14	(10.2%)	35	20	(57.1%)	46	1	(2.2%)	13	2	(15.4%)
Anaplastic	131	9	(6.9%)	16	5	(31.2%)	56	—	(—)	6	—	(—)
Unclassified	55	9	(16.4%)	2	1	(50.0%)	25	—	(—)	—	—	(—)
Adenocarcinoma	28	1	(3.6%)	6	5	(83.3%)	16	—	(—)	5	2	(40.0%)
Totals	454	48	(10.6%)	59	31	(52.5%)	196	1	(0.5%)	24	4	(16.7%)

*Based on 220 cases in which diagnosis was made 5 yr. or more before close of study.

will survive for more than a year without resection whereas 42.6 per cent survive for one or more years with resection. Thus, if it is possible to remove a tumor and there are no other known metastases the prognosis is significantly better than if resection is not possible.

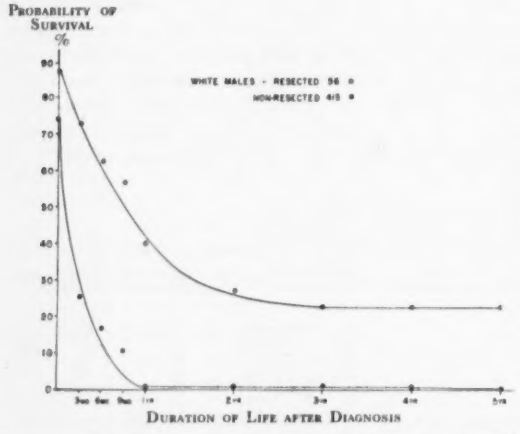

FIGURE 3. *Probability of Survival during Specific Period Plotted from a Life-Survival Table.*

All cases were followed for at least a year and were withdrawn from the study only because the date of operation or diagnosis was less than five years before the close of the study. The risk of death within a five-year period was so great that the effect of age was ignored.

It is recognized that the character of the tumor is a most important factor in prognosis. It seems permissible to speculate that the lesions that can be resected include a higher percentage of the less malignant tumors.

Excluding postoperative deaths, 49 patients survived lobectomy or pneumonectomy, and the results in these and were followed for five years, none with lymph-node involvement were alive. Four of 12 without lymph-node involvement, or 33 per cent, survived for five years or more. The presence of metastasis in lymph nodes at the time of operation indicates a poor opportunity for a long-term survival.

Discussion

This study indicates that 70 per cent of the patients with bronchogenic carcinoma seen at the Albany Hospital from 1936 through 1951 were already in such an advanced state that definitive surgical treatment was contraindicated. Furthermore, there is no evidence from this study that the incidence of operability is increasing. The fact that so many patients have an initial symptom that is probably extrabronchial in origin indicates that lay or medical education can contribute little to earlier diagnosis. In the cases of squamous-cell carcinoma, however, there is a high incidence of bronchial symptoms as the initial complaint, and it is in this group that one can expect to improve the survival rate by earlier diagnosis and more prompt surgical treatment. Even though the present five-year survival rate is quite low surgery offers the only method of cure and perhaps the best method of palliation. If surgical resection is feasible the improved one-year survival rate indicates that this measure is worth while in terms of palliation. It is possible that improved methods of diagnosis, such as cytologic studies in patients with expectoration and roentgenographic studies in asymptomatic cases, will raise a suspicion of cancer earlier in the course of the disease. This prospect is good in the group of squamous-cell carcinomas, which comprise 172 cases, or 33.2 per cent of the total. Cytologic studies were done in many of the cases in this study after pulmonary cancer had been suspected, but it is frequently too late at this period.

In this study there was an absolute five-year cure rate of 5.8 per cent in adenocarcinomas (2 cases), but this group comprises such a small part of the whole that it contributes little to the main problem of bronchogenic carcinoma. Indeed, others[5,9] have not noted similar results in the treatment of adenocarcinoma.

Routine x-ray examinations revealed only 8 cases, or 1.6 per cent, of the total in this series, a depressingly low figure in view of the large number of x-ray surveys in New York State. It has been difficult to persuade patients with asymptomatic pulmonary lesions to submit to study and possible thoracotomy, which is often required for diagnosis.

It is also of interest that in a review of the initial roentgenograms in this series, 25 patients, or 4.9 per cent of the total, had normal posteroanterior chest films at the time of diagnosis. Except for peripheral lesions routine roentgenographic examination of the chest is of limited value.

SUMMARY

Five hundred and seventeen cases of bronchogenic carcinoma are reviewed and classified according to histologic type. Squamous-cell carcinoma was the most common classification.

Forty cases were seen in the period 1937-41, and 320 cases in the period 1947-51.

Ninety-three per cent of cases were in males and 7 per cent in females. The lowest ratio of males to females was in the group of adenocarcinomas (2.7:1).

The initial and other symptoms are tabulated. Squamous-cell carcinoma appears more likely to cause initial bronchial symptoms than any of the other cell types.

The commonest site for the primary tumor was in the upper lobes and on the right side.

Anaplastic tumors could be measured in the roentgenogram in 40.8 per cent of cases, adenocarcinomas in 35.3 per cent, and squamous-cell carcinomas in 24.4 per cent. Forty and one-tenth per cent of squamous-cell carcinomas, 35.3 per cent of adenocarcinomas, and 29.9 per cent of anaplastic carcinomas were considered "operable" at diagnosis. Fifty-two and two-tenths per cent of squamous-cell carcinomas, 50.0 per cent of adenocarcinomas, and 38.8 per cent of anaplastic carcinomas could be resected.

The operative mortality for pneumonectomy is 17.8 per cent for the entire series but decreased to 7.1 per cent in the last two years of this study. There were no operative deaths from lobectomy in 12 cases.

Fifteen and four-tenths per cent of the patients survived for a year from the date of diagnosis; 10.6 per cent survived for a year without resection, and 52.5 per cent survived for a year after resection.

In 220 cases in which the diagnosis was made over five years before the termination of this study 5 patients, or 2.3 per cent, survived for five years or more; 4 of 19 (21.1 per cent) patients operated on lived for five or more years after operation.

There were 3 five-year survivors with squamous-cell carcinoma, and 2 with adenocarcinoma.

No patient with known lymph-node metastasis at the time of pulmonary resection survived for five years.

We are indebted to Miss Rita Cashman and Mr. Arthur Kraus, of the Statistical Staff of the Bureau of Cancer Control, New York State Department of Health, for valuable assistance in the collection of data and advice in the methods of analysis; to Miss Dorothy Lasher for secretarial aid; to Dr. Arthur Wright, professor of pathology at Albany Medical College, and members of his staff for help in obtaining pathological data; to Mrs. Ruth Koster, medical-record-room librarian at the Albany Hospital, and her staff for hospital records and aid in the completion of this study; to Miss Marilyn McCully for the illustrations and tabulations; and to Dr. L. Whittington Gorham, formerly professor of oncology at Albany Medical College, for stimulus in the organization and initial planning of this study.

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AMPUTATION NEUROMA OF THE BILE DUCTS WITH OBSTRUCTIVE JAUNDICE*

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BOSTON

AN amputation neuroma may form from the cut ends of nerve fibers divided in the course of surgery on the biliary tree, just as it may occur elsewhere in the body. A tumor results that is not a true neoplasm but is made up of masses of interlacing axons, intermixed with scar tissue. Various observers have reported the presence of Schwann sheath cells in these amputation neuromas. The occurrence of such Schwann cells is reasonable since the afferent pain

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impulses from the biliary tree are carried by myelinated visceral fibers, which travel with the nonmyelinated motor autonomic nerves and eventually enter the spinal cord through the dorsal roots. Since these afferent fibers have sheaths Schwann cells should be available to participate in neuroma formation in the region of the bile ducts.

Husseinoff[1] reported the incidental autopsy finding of a neuroma involving the cystic-duct stump in 1929, and Shapiro and Lifvendahl[2] described a similar finding in 1931. Cieslak and Stout[3] presented a series of traumatic and amputation neuromas in 1946, including 1 case that followed cholecystectomy. Womack and Crider,[4] writing in 1947, reported 6 cases in which pain persisting after cholecystectomy was attributed to a neuroma arising from nerve fibers divided in the region of the cystic duct. Troppoli and Cella[5] have more recently presented 2 similar cases.

The first description of common-duct obstruction and jaundice resulting from an amputation neuroma of the cystic duct was made by Comfort and Walters[6] in 1931. The involved portion of the duct was successfully resected in this case. Stembridge[7] reported a case in which biliary obstruction and mild jaundice developed because of a neuroma that followed cholecystectomy with probably accidental injury to the common bile duct.

The 2 cases reported below illustrate the development of a high degree of biliary obstruction, with deep jaundice, associated with the formation of an amputation neuroma that followed surgery on the biliary tree.

Case Reports

Case 1. O.A. (M.G.H. 377979), a 48-year-old woman, was admitted to the hospital on January 28, 1948, because of anorexia and nausea of 2 weeks' duration accompanied by a weight loss of 9 pounds. Five days before admission she was noted to be jaundiced, and the next day she had a chill with a fever of 101.6°F. Daily elevations of temperature had continued, but there had been no further chills. Stools and urine had been normal in color. She had some discomfort in the right upper quadrant of the abdomen, but no pain.

In 1936 a cholecystectomy had been performed at another hospital for chronic cholecystitis and cholelithiasis. During the course of the operation the common duct had been accidentally divided. This had been immediately recognized, and the duct resutured. Except for a transient episode of jaundice 4 years later, she had remained in good health until the present illness.

Physical examination was not remarkable except for mild jaundice and a liver edge that extended 3 fingerbreadths below the right costal margin and was sharp and moderately tender. The spleen could not be felt.

Examination of the blood showed a hemoglobin of 13.0 gm. per 100 cc. and a white-cell count of 13,800, with 90 per cent neutrophils. The urine gave a ++ test for bile. The fasting blood sugar was 92 mg., the nonprotein nitrogen 28 mg., the serum bilirubin 4.4 mg. direct and 6.0 mg. total, and the total protein 7.7 gm. per 100 cc., with an albumin-globulin ratio of 1.4. The prothrombin time was 15 seconds (control, 16 seconds), and the alkaline phosphatase 21.7 Bodansky units. Cephalin flocculation was negative in 24 and 48 hours. The serum cholesterol was 582 mg. per 100 cc. (esters 319 mg.); thymol turbidity was 0. X-ray studies of the gastrointestinal tract with barium did not reveal any abnormality.

On the 5th hospital day a needle biopsy of the liver showed biliary cirrhosis. The stools remained brown and contained bile. Duodenal drainage done on the 12th hospital day demonstrated many calcium bilirubinate crystals, many white cells, which were not bile stained, and a rare cholesterol crystal.

Starting on the day of the liver biopsy daily temperature elevations to 101 to 103°F. occurred, with occasional chills. The serum bilirubin rose to 31 mg. per 100 cc. direct (45 mg. total) by the 12th hospital day, and the hemoglobin fell to 9.0 gm. per 100 cc. Three 500-cc. blood transfusions were given. The first acholic stool appeared on the 16th hospital day. The alkaline phosphatase had risen to 35 Bodansky units. The prothrombin time remained normal.

Twenty days after admission abdominal exploration was carried out. The portal vein, hepatic artery and common bile duct were identified after a prolonged dissection. The common duct was smaller than normal, its wall was thickened, and the lumen admitted only a 4-mm. dilator, which passed easily into the duodenum. With a 3-mm. dilator as a guide the upper duct was dissected from surrounding scar tissue and traced up into the liver, where the lumen was occluded and could not be traced farther. No bile-filled structure could be found by needle aspiration. Attempts to probe the obliterated lumen of the duct produced moderate bleeding. A small T tube was placed in the common duct, and the abdomen closed. The patient died within 24 hours in spite of multiple transfusions and other supportive measures.

Autopsy showed that the cause of death was hemorrhage into the abdominal cavity presumably from the region of the porta hepatis although the exact site could not be determined. The common hepatic duct was completely obstructed within the liver by a neuroma, which surrounded the duct. The intrahepatic bile ducts were moderately dilated on the left and only slightly so on the right. They contained only small amounts of bile. The liver showed bile stasis and early biliary cirrhosis.

The twelve-year interval between the time of surgery on the cystic and common bile ducts and the development of jaundice indicates the leisurely rate of growth that such an amputation neuroma may have. The entire episode, involving the rapid development of deep jaundice, was painless. The lack of dilated, bile-filled, intrahepatic biliary passages was an unusual feature of this case. The immediate cause of death was postoperative hemorrhage, almost surely from the region of the porta hepatis, resulting from efforts to locate a bile-containing structure in this region by aspiration. On microscopical examination the obstructing process had the histologic characteristics of an amputation neuroma (Fig. 1).

Case 2. E.M. (M.G.H. 819646), a 60-year-old man, was admitted to the hospital on August 3, 1953, because of fatigue and anorexia of 2 months' and jaundice and dark urine of 6 weeks' duration. The stools had been noticed to be light in color more recently. He had had no pain, chills or fever at any time.

Five years previously a cholecystectomy and choledochostomy had been performed at another hospital. Stones were found in the gall bladder. The postoperative course was uncomplicated, and he had been entirely well until the present illness.

Physical examination disclosed deep jaundice and a firm, nontender liver edge at the level of the umbilicus.

Examination of the blood revealed a hemoglobin of 14.0 gm. per 100 cc. The urine gave a ++ test for albumin and a ++++ test for bile. A stool was negative for bile and gave a negative guaiac reaction. The total protein was 6.7 gm. (albumin-globulin ratio, 1.6), and the serum bilirubin 19.6 gm. per 100 cc. The prothrombin was 83

per cent. The alkaline phosphatase was 45.9 Bodansky units, and the serum cholesterol 788 mg. per 100 cc.

At operation on August 7 the common bile duct was identified; it was normal in size. As it was followed upward a hard nodule, 2 cm. in diameter, was encountered at the level of the porta hepatis. This completely surrounded the duct and at first was thought to be a primary carcinoma of the bile duct. As the dissection progressed, however, it was possible to free the tumor from the liver and to develop a 2-cm. cuff of dilated but otherwise normal common hepatic duct above the point of obstruction. The duct was opened below the tumor. Dilators passed easily downward into the duodenum but could not be passed upward. An excision of the portion of the duct containing the tumor was done, with an end-to-end suture of the duct. A T tube was placed in the duct below the anastomosis, with the upper arm extending upward beyond the suture line.

Pathological examination of the specimen showed an amputation neuroma surrounding a dilated stump of cystic duct with secondary occlusion of the common duct (Fig. 2).

The postoperative course was uneventful. A cholangiogram taken 10 days after operation was normal except for dilatation of the biliary radicles. The T tube was left in place for 6 months. The patient has remained well without symptoms of biliary obstruction or cholangitis.

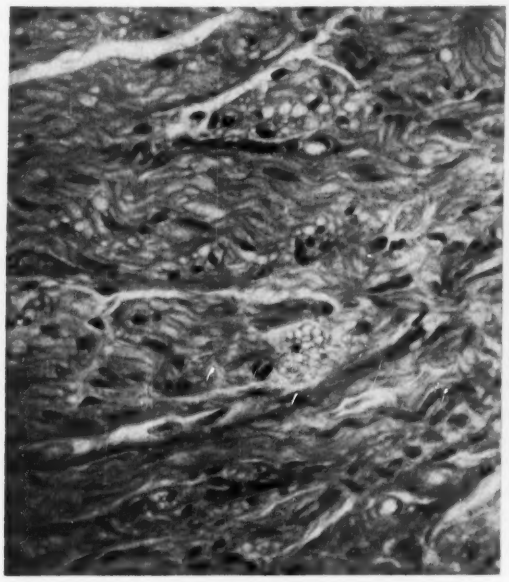

FIGURE 1. *Photomicrograph of the Neuroma in Case 1. The picture is that of the so-called "amputation neuroma," with masses of nerve fibers intermixed with fibroblasts.*

Again, the long interval between the operation on the cystic duct and the development of obstruction owing to an amputation neuroma was a striking feature of this case. There was no pain during the entire illness. Fortunately, this lesion was so situated that a satisfactory resection could be done.

DISCUSSION

The formation of amputation neuromas after biliary-tract surgery is a well recognized entity. In fact, many attempts have been made to implicate these neuromas as the cause of the symptoms that occasionally follow or persist after cholecystectomy.

The unusual features of the 2 cases reported above were the development of a high degree of biliary obstruction many years after biliary-tract surgery and the complete absence of pain. In each case an amputation neuroma was demonstrated to be the cause of the obstruction, and histologic examination of the specimen was obtained. Such an amputation neuroma

FIGURE 2. *Photomicrograph of the Obstructing Lesion in Case 2.*

The interlacing bundles of axons and fibroblasts are clearly shown.

consists of a mass of tissue composed of interwoven axons and fibrous tissue. It is a benign process that may be amenable to surgical correction if the technical problems are not insurmountable.

Although rare, an amputation neuroma must be considered in the differential diagnosis of any patient who has had a previous operation on the biliary tree and in whom obstructive jaundice develops. The recognition of this entity may obviate unnecessarily radical surgery.

SUMMARY

Two cases are reported in which the development of painless jaundice many years after biliary-tract surgery was shown to be associated with the formation of amputation neuromas that obstructed the bile ducts.

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A NEW SEDATIVE (ANTIPSYCHOMOTOR) DRUG USEFUL IN LABOR*

Preliminary Report

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THE ideal pharmacologic agent to manage the problem of pain relief in labor has yet to be developed. It should provide complete comfort for the mother and absolute safety for the baby without any essential alteration of the course of labor. The staff at the Boston Lying-in Hospital has taken an active interest in this problem for many years. Our most successful methods of obstetric amnesia and analgesia involve the use of limited amounts of barbiturates early in labor and scopolamine. However, this therapeutic regimen in about 5 to 10 per cent of cases may be associated with an undesirable side effect of increased psychomotor activity related to the barbiturates and scopolamine. The occurrence of increased psychomotor response becomes progressively more active with the progress of labor.

We recently had the opportunity to observe the antiemetic effects of a new synthetic drug, chlorpromazine. Its effectiveness in vomiting states encountered in pregnancy is to be the subject of a report now in preparation. A chance observation in a patient who had annoying vomiting in labor suggested to one of us (D.E.R.) that the drug might have specific merit as a pharmacologic antagonist to the psychomotor hyperactivity induced by the barbiturates and scopolamine. The intramuscular administration of 12.5 mg. of the drug had a prompt antiemetic effect, and, in addition, the patient became drowsy and quiet. Her subsequent eight-hour labor was managed with repeated small doses of scopolamine and one additional dose of chlorpromazine. She remained entirely comfortable.

This communication is regarded as a preliminary report on the use of the drug in labor, for it involves 100 cases. The group studied was divided equally between primiparous and multiparous patients. The ages varied from seventeen to thirty-eight years, the majority of patients being in the third decade of life. The height of the patients varied from 150 to 170 cm., and the weight immediately before onset of labor from 54 kg. (120 pounds) to approximately 91 kg. (200 pounds). The gravidity was from 1 to 7 and the parity from 0 to 5. Most of the patients were at or near term. The prenatal complications were confined to anemia in some cases, Rh incompatibility in a few and asthma or other allergic manifestations in 2.

Description

The drug‖ is known in the United States as compound SKF 2601-A, chlorpromazine and Thorazine. It was originally developed by the Rhône–Poulenc Special Research Laboratories in France as compound 4560 R.P. and labeled Largactil. It is a synthetic chlorinated derivative of phenothiazine. Its chemical designation is 10-(alpha-dimethylamino propyl)-2-chlorophenothiazine hydrochloride. Its structural formula was recently given in this journal.[1] It is freely soluble in water at room temperature but is somewhat photosensitive. We employed a 2.5 per cent aqueous solution (25 mg. per cubic centimeter) with a pH value of approximately 4.9.

Action in Human Beings

It should be emphasized that chlorpromazine had a background of extensive experimental and clinical investigations in other fields before the present study was undertaken. The most prominent clinical effects are discernible on the psyche and the nervous system. The drug was successfully used as an inhibiting agent[2] for the control of various states of mental agitation.

The action on the central nervous system is quite diversified. In addition to its sedative property, it possesses an antiemetic[3] and a hypothermic effect[4]; as a consequence it has been employed to produce artificial hibernation. It also has the capacity of potentiating the effects of the anesthetic and analgesic agents.

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‖We are indebted to the Smith, Kline and French Laboratories, Philadelphia, for providing a constant supply of the drug in the form of Thorazine.

In fact it is used by some clinicians to produce narcosis in the form of a "lytic cocktail." However, one must be cautious in applying an anesthetic agent that potentially can cause hypotension as well as hypothermia. Peripherally, it has been observed to act as a sympatheticolytic (antiadrenergic) as well as a parasympatheticolytic agent. These many and varied actions on the nervous system have resulted in its being referred to as a "neuroplegic" agent. The obstetric patient under the influence of chlorpromazine appears to take an objective attitude toward her immediate course and environment during labor.

The cardiovascular effects of the new drug are multiple, but its chief action tends to induce a variable hypotensive state. A compensatory tachycardia frequently accompanies the hypotensive effect. However, we have observed bradycardia in some cases. Respiration does not seem to be affected unless other depressant drugs, even in smaller dosage, are administered simultaneously.

A reported undesirable side effect is the reversible impairment of liver function when the patient is exposed to large doses for prolonged periods. An allergic response, even though the drug is related to certain antihistaminic drugs, has occasionally been noted. Dryness of the mouth and flushing or pallor of the face have been observed. Extreme caution must be exercised when other central depressant drugs are administered simultaneously. The incidence of catheterization required in the post-partum period has been considerably reduced under the influence of chlorpromazine. The undesirable systemic effects and local signs (such as irritation and thrombosis) are likely to appear where the drug is injected intravenously.

Chlorpromazine has been employed both for preanesthetic medication and as a total anesthetic agent.* It should not be administered with morphine, or morphine-like drugs, for the antidiuretic action of morphine is increased while the central depressant action of this group of drugs is potentiated. Chlorpromazine has been used in the treatment of postoperative hiccups as well as postoperative, post-traumatic and postpartum delirium. It has a diversity of nervous-system responses, variability in individual responsiveness, a potentially high degree of effectiveness and a comparatively low degree of toxicity. Regardless, one should resist the temptation to overdosage and indiscriminate therapeutic application under all circumstances.

Administration During Labor

At the Boston Lying-in Hospital the assistant resident on duty orders the medication for the obstetric patient in labor. The actual administration of the drugs is carried out by the nursing staff.

The early efforts involved doses of 12.5 mg. to 25 mg. given intramuscularly at about two-hour intervals. The total dosage for an individual labor was limited, with 1 exception, to 100 mg. Primiparous patients were selected for this particular evaluation in the series. The patients were usually drowsy or slept between contractions and were awake during the contractions. As labor progressed most mothers were uncomfortable and conscious, with variable degrees of pain and with no evidence of amnesia. The course of labor was not altered. The infants responded promptly at birth, with good reflex activity. All the patients in this pilot group would have preferred more complete medication during labor.

Another pilot study was made in which scopolamine (0.3 mg.) was combined with chlorpromazine as previously outlined. The patients had somewhat more relief during labor but would have desired more satisfactory medication throughout their labors. Amnesia, partial or incomplete, was present in this group. The course of labor was unchanged. The babies revealed good reflex irritability at birth.

Other pilot studies were made with the addition of one early dose of 90 or 180 mg. of Seconal or Seconal (180 mg.) in conjunction with Amytal (180 mg.) or Demerol (50 mg.) or Dilaudid (0.15 to 0.3 mg.). These were tried with and without scopolamine added to the same basic doses of chlorpromazine. Seconal (90 mg.) combined with chlorpromazine either alone or with atropine sulfate gave results comparable to those with chlorpromazine alone. Seconal and Amytal, 180 mg. of each, supplemented by chlorpromazine produced central-nervous-system depression of sufficient degree so that in one pilot study 30 per cent of mothers were able to tolerate an artificial airway. The infants in this group of patients were active and responded promptly, more so than in another series, in which Demerol (50 mg.) in several doses at two-hour intervals was administered in conjunction with chlorpromazine. Chlorpromazine (100 mg. in divided doses) supplemented with Dilaudid (0.15 mg.) proved as unsatisfactory as the new agent alone, or in combination with one dose of atropine (0.3 to 0.6 mg.) in attempts to provide either relief of pain or amnesia. Various other combinations were investigated. Finally, we evolved a plan of administration of Seconal, scopolamine and chlorpromazine in which amnesia and analgesia were satisfactory, psychomotor activity controllable and the labor room comparatively quiet. Moreover, the method provided safety for both mother and baby. The administration of adequate amounts of chlorpromazine is essential to its effective use.

To obviate too great a discrepancy in the administration of the drugs (Seconal, scopolamine and chlorpromazine) employed, and to permit adjustment of dose and time factors in relation to variations in individual maternal reflex irritability, the regimen outlined in Table 1 is presently employed. This approach was used in the majority of the cases on which the current preliminary report is based.

*Caution must be exercised when the drug is employed with other central-nervous-system depressants.

Seconal was selected as the barbiturate of choice for psychic sedation. It not only is a member of the short-acting barbiturates but also has never been involved in respiratory accidents or deaths at this hospital. Seconal and scopolamine have given quite satisfactory amnesia analgesia during labor.

Evaluation of the Method

Most patients were delivered normally or by the application of outlet forceps and median episiotomy. The Scanzoni maneuver was performed in 3 cases, and mediolateral episiotomy in selected cases.

Each patient was interviewed soon after emergence from anesthesia, on the following day and at various subsequent periods during her post-partum hospital stay to evaluate the effectiveness of the drugs during her labor. Most patients cannot differentiate amnesia and analgesia; for this reason the term amnesia analgesia is used.

The majority of the women had satisfactory amnesia analgesia soon after the second injection of scopolamine and chlorpromazine. Practically all primiparous patients were pleased with the result during labor. Many multiparas volunteered the information that this regimen was more satisfactory than any other pharmacologic management experienced in previous labors. Many patients, both primiparas and multiparas, would have liked the regimen of medication to be instituted earlier in their labor.

The total dose of chlorpromazine used in any case was limited to approximately 100 mg. In 1 case 187.5 mg. was administered. The number of doses varied from a minimum of 1 to a maximum of 13. The average and usual dose was 12.5 mg., and the largest single dose was 25 mg. The intramuscular route was ordinarily employed. The average effective therapeutic dose was the second in accordance with the regimen outlined.

The anesthesia used for delivery was an inhalational procedure in most cases, nitrous oxide, oxygen and ether being used in sequence. Low spinal block, so-called saddle block, was employed in selected cases. A few patients had pudendal block in which nitrous oxide and oxygen were frequently given as a supplemental procedure. When the patient had been adequately medicated to the recommended amount little inhalation anesthesia was required. The emergence phase was pleasant and uneventful. The condition of the babies at birth was impressively satisfactory. They had good reflex irritability, good muscle tone and spontaneous respiration at or soon after delivery in 96 per cent of the cases; there was no evidence of respiratory or cardiac depression, even when the total amount of the drug was 75 mg. or more. Resuscitative measures were required for two or more minutes in 4 per cent of cases for the following reasons: prolonged second stage with right occiput posterior position required a Scanzoni maneuver for delivery—the mother received a total amount of 37.5 mg. of chlorpromazine during labor; the second mother had edema and anemia as prenatal complications, with labor induced by artificial rupture of the membranes, a total of 37.5 mg. of chlorpromazine being used; in another case, in which there was partial prolapse of the cord, with a segment of cord tight around the infant's neck, the mother received a total of 25 mg. of chlorpromazine during her labor; and the fourth mother required a forceps rotation at the time of delivery, but she received two doses of Dilaudid totaling 0.6 mg. in addition to 25 mg. of chlorpromazine.

Table 1. *Preanesthetic Medication for Uncomplicated Labor When Vaginal Delivery is Expected.*

Period	Purpose	Drug	Dosage mg.	Route	Time of Administration
I	Psychic sedation	Seconal	180.0	Oral or rectal	Early in established labor (after admission enema)
II	Amnesia & analgesia				
	A Initial medication	Scopolamine	0.4	Intramuscular	When patient first complains of pain (usually ½ to 1 hr. after I)
		Chlorpromazine*	25.0	Intramuscular	
	B Second medication	Scopolamine	0.3	Intramuscular	2 hr. after A & every 2 hr. thereafter
		Chlorpromazine*	12.5	Intramuscular	
III	Intermediate medication (especially in patients with increased psychomotor activity)	Chlorpromazine*	12.5	Intramuscular	As indicated

*Contraindicated in patients with cardiovascular, respiratory, hepatic, renal or metabolic complications.

The observation in the last case points up the necessity of caution in the administration of repeated doses of central-nervous-system depressants in addition to chlorpromazine during labor. It should also be remembered that factors besides medication during labor and anesthesia for delivery operate to reduce the reflex irritability of the newborn.

Summary and Conclusions

A new drug, chlorpromazine (compound SKF 2601-A), is shown to possess distinct merit as an addition to the agents employed in the management of

labor. It has no amnesic value when used alone during labor.

The new preparation, employed in the regimen outlined, has distinct value for the mother during labor, and in this series no ill effects on the fetus were encountered.

Its value appears to be as a pharmacologic antagonist to psychomotor hyperactivity periodically encountered in the use of scopolamine in labor.

A recommended regimen of medication during labor employing a barbiturate as a psychic sedative, scopolamine as an amnesic agent and chlorpromazine as a psychomotor antagonist is considered. The quieting effect on the patient is impressive.

There is much to be learned about the clinical pharmacologic effects of chlorpromazine and its proper dosage. Further investigation of the application of this new drug to obstetric patients is recommended.

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BACTERIAL ENDOCARDITIS DUE TO A PENICILLIN-RESISTANT STAPHYLOCOCCUS*

Report of a Case Successfully Treated with Erythromycin, Oxytetracycline and Streptomycin

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THE following report of a patient with staphylococcal endocarditis is presented to illustrate the difficulties encountered in the treatment of this disease and to describe the use of large amounts of erythromycin, which appeared of benefit in achieving a cure.

R.B.B., a 3-year-old boy, with a defect of the intraventricular septum, became acutely ill on October 29, 1953, with malaise, anorexia, chill and high fever. A small penile ulcer had been noted several days previously. He was given chlortetracycline at home but continued to have recurrent bouts of chills and fever when he was admitted to the hospital on November 2.

Physical examination revealed a pale, irritable and acutely ill boy with a temperature of 105°F. by rectum. The pulse rate was rapid. No petechiae or signs of embolism were found. The lungs were normal. The heart was of normal size. There was a systolic thrill palpable at the left sternal border. A loud systolic murmur was audible in the 3d and 4th left intercostal spaces in the parasternal line. The spleen was felt 2 cm. below the left costal margin. The weight was 13.6 kg.

Examination of the blood disclosed a red-cell count of 3,600,000, with a hemoglobin of 9.9 gm. per 100 cc. and a sedimentation rate of 88 mm. per hour; the white-cell count was 33,400, with an increased number of immature neutrophils. Urinalysis was normal except for a trace of albumin and 2 to 8 white cells per high-power field in the sediment. Blood cultures obtained on November 3, 4, 11, 13 and 14 demonstrated hemolytic *Staphylococcus aureus*, coagulase positive. Sensitivity tests on the organism cultured on November 4 and 11 showed that bacterial growth was grossly inhibited by 5 units of penicillin, 12.5 microgm. of streptomycin, 0.7 microgm. of chlortetracycline and oxytetracycline, 0.37 microgm. of erythromycin and 3.1 microgm. of chloramphenicol per cubic centimeter. However, when the erythromycin-containing culture tube was subcultured on blood-agar plate, growth occurred. On December 15 the hemoglobin value was 10.8 gm. per 100 cc., and the white-cell count was 11,600, with a normal differential count; urinalysis was normal. On February 3, 1954, the hemoglobin was 12.2 gm. per 100 cc.; erythrocyte, leukocyte and platelet counts were normal. An electrocardiogram was normal except for sinus tachycardia. X-ray study of the chest revealed the heart to be borderline in size.

On November 4 antibiotic therapy was initiated with massive intravenous doses of penicillin and streptomycin intramuscularly. In spite of 60,000,000 units of penicillin and 0.25 gm. of streptomycin daily the chills and fever (temperatures ranging to 104°F.) continued unabated, and the patient remained critically ill.

After 5 days penicillin was discontinued, and blood cultures again revealed the offending staphylococcus. Erythromycin orally and streptomycin failed to sterilize the blood cultures; oxytetracycline was then substituted for streptomycin. On this combination the febrile state became less erratic, and the chills decreased. On November 18 erythromycin tablets were found passing undissolved in the stools, and another chill occurred. Erythromycin§ for injection was administered by means of a constant intravenous infusion, 2 gm. daily, through a polyethylene venous catheter, with additional booster doses of 250 mg. of erythromycin injected intravenously every 8 hours, concurrently with 1 gm. of oxytetracycline intravenously each day. One week after its omission streptomycin was resumed. On this regimen the fever further abated, but the temperature continued to rise to a daily maximum of 102°F. At this time the patient appeared much improved. Considerable edema and tenderness developed proximal to the venous cut-down sites. After 12 days, erythromycin and oxytetracycline were resumed orally, and the intravenous injections were discontinued. The low-grade fever subsided entirely thereafter, lending support to the belief that the phlebitis was responsible. With the improvement in temperature the appetite progressively increased, and the patient appeared much brighter and happier. During subsequent weeks of oral medication intermittent diarrhea appeared, and occasionally undigested erythromycin passed in the stools, but this was controlled with opiates and tablets of lactobacilli by mouth. The streptomycin (alternated with dihydrostreptomycin) was reduced in amount and then omitted because of the appearance of ataxia. The ataxia gradually cleared com-

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§Kindly supplied as Ilotycin for intravenous use by the Eli Lilly Research Laboratories, Indianapolis, Indiana.

pletely during the ensuing 2 weeks. The spleen remained palpable until discharge from the hospital on December 17. Erythromycin and oxytetracycline were continued at home in doses of 2.0 and 1.0 gm. daily until January 18, 1954, when all antibiotics were discontinued. The clinical improvement persisted, and the spleen became smaller. As of April there had been no recurrence of fever or other symptoms, and blood cultures were repeatedly sterile. The temperature graph and daily antibiotic dosage are presented in Figure 1.

Discussion

This child had staphylococcal endocarditis superimposed on a defect of the ventricular septum. Massive doses of penicillin (30,000,000 to 60,000,000 units daily) intravenously and streptomycin intramuscularly had no effect. The temperature appeared to respond to the combination of streptomycin, erythromycin and

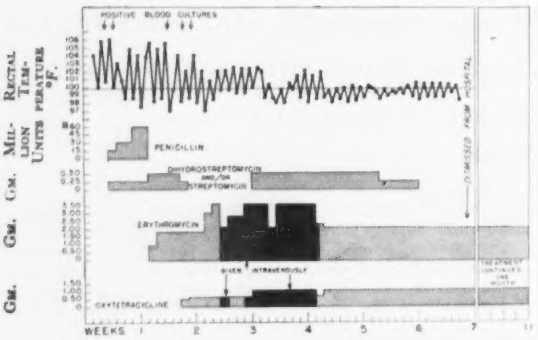

Figure 1. *Effect of Various Combinations of Antibiotics.*

oxytetracycline when the last two drugs were given by mouth. But with the appearance of diarrhea, which was apparently due to the oral medications, the drugs were incompletely absorbed, and the patient appeared to relapse symptomatically. When oxytetracycline and large doses of erythromycin were given intravenously impressive clinical improvement and decrease in fever followed. Slight fever persisted because of severe phlebitis at the venous cut-down site, until the oral route was again used. Subsequently, improvement was maintained, and periodic diarrhea could be easily controlled. Because of the combination of agents used no single drug can be credited with the cure; indeed, the combination itself may have been essential.

This is believed to be the largest reported quantity of erythromycin given intravenously, on the basis of body weight; the dosage was relatively much greater than that used in other cases of staphylococcal endocarditis reported. No toxic effects were observed except for a local burning sensation along the course of the veins injected and the development of phlebitis. However, the drugs were administered for five and seven days respectively in two different arm veins, with the aid of small amounts of heparin in the infusion solution.

The responsible organism was inhibited in vitro by a concentration of penicillin easily obtained in vivo by large doses of penicillin given parenterally. It is of interest that such doses were exceeded many times and yet no clinical effect was apparent during the administration of the antibiotic. The organism was also cultured while the patient received moderate doses of erythromycin, which appeared to be beneficial at much greater doses. Such findings point up the inadequacy of ordinary antibiotic inhibitory tests in predicting a clinical response to therapy.

There is now considerable evidence that the bacteriostatic agents, chlortetracycline, oxytetracycline and chloramphenicol, rarely cure bacterial endocarditis.[1,2] Erythromycin alone, in ordinary doses, likewise appears undependable in this regard.[2-4] The bacteriocidal agents, penicillin, streptomycin and bacitracin, have been most consistently effective when used in combinations.[2] The increasing frequency with which one encounters staphylococci resistant to single antibiotics calls for more effective combinations in dealing with this form of endocarditis. The experience with this case suggests a synergistic effect of other agents with erythromycin. Furthermore, the unusually large dose of erythromycin given intravenously and orally may have been effective. Jones and Yow[3] reported 1 case of staphylococcal endocarditis, 3 of streptococcal endocarditis and 1 of endocarditis of unknown etiology in which cure was obtained with a combination of erythromycin and streptomycin, and also a case of enterococcal endocarditis in which administration of erythromycin and bacitracin resulted in cure whereas erythromycin alone in the usual doses was ineffective. Recently, Geraci and Martin[4] described 4 cases of staphylococcal endocarditis in a series of 7 patients with endocarditis of varying etiology treated with erythromycin. All 4 patients died in spite of therapy. However, the doses of erythromycin were not in the high range here reported, nor were the drug combinations used that were successful in this case, although in vitro tests with erythromycin and streptomycin were subsequently performed and a synergistic effect of these agents against the offending staphylococcus was demonstrated. Erythromycin, in large doses, combined with streptomycin and oxytetracycline, was curative in the present case, and this combination appears to merit further trial in endocarditis caused by resistant staphylococci.

Summary

A case of congenital heart disease in a child with a defect of the intraventricular septum and superimposed endocarditis caused by a resistant staphylococcus is presented. A cure was achieved by means of very large doses of erythromycin in addition to streptomycin and oxytetracycline. Erythromycin intravenously appeared to be of benefit and was apparently used in the largest dose reported for a child.

No toxic effects besides local phlebitis at the injection site were encountered.

Further trial of large doses of erythromycin, and the combination of erythromycin with streptomycin and oxytetracycline for staphylococcal endocarditis appears worth while.

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MEDICAL PROGRESS

ACTH AND CORTISONE THERAPY OF RHEUMATIC FEVER AND RHEUMATIC CARDITIS (Continued)*

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Pericarditis. Data on the effect of cortisone or ACTH on this serious and obvious manifestation of rheumatic inflammation of the heart have been collected for 64 cases reported by 18 groups of investigators.[4-6,11,18-21,24,27,29,30,35,38,40,43,44,46,49] The duration of the pericarditis after the beginning of therapy in these cases (usually indicated by the duration of a pericardial friction rub) is summarized in Table 1.

In 6 fatal cases the signs of pericarditis continued until death. However, death occurred in 1 of these within twelve hours and in another within thirty-six hours of the beginning of treatment—long before there had been an opportunity for the hormones to have any appreciable influence on the disease process.

In 1 patient a pericardial friction rub was heard for the first time during therapy, but in 3 others described by the same authors[40] signs of pericarditis persisted during therapy. It is to be noted, however, that these 4 patients were treated with only 50 mg. of lyophilized ACTH a day and for a period of only eight days.

The signs of pericarditis disappeared during therapy in all the other 54 patients (84 per cent of the total) within one to seven days in 24 (71 per cent) and within eight to fourteen days in 9. In only 1 patient did they last longer than fourteen days; duration was not recorded in 20 patients.

Even if the 6 patients who died and the 4 patients in whom pericarditis did not disappear during treatment are added to the 34 patients for whom information on duration of signs is available, it is evident that of a total of 44 patients thus obtained pericarditis subsided within seven days in 24, or 55 per cent. The apparent rapidity of the favorable influence is further indicated by information concerning the exact duration of the manifestations in 19 of the 24 cases. Pericarditis subsided within one to seven days in those for whom such information could be obtained. These data (not included in the table) show that in 16 of the 19 patients the signs of pericarditis disappeared within one to four days.

Obviously, the significance of these various figures depends on the rapidity and completeness with which pericarditis would have subsided in the same patients if they had not been treated with hormones. Since this information is not available, final conclusions are not completely justified. Nevertheless, in the light of previous experience with similar cases, it seems highly unlikely that without hormone therapy so many patients would have improved as rapidly as was observed in this series of collected cases. Therefore, even though final conclusions cannot be made, it can be said that the data reviewed here strongly suggest that rheumatic pericarditis is suppressed by cortisone and ACTH.

TABLE 1. *Time Required for Disappearance* of Pericarditis after Beginning of Treatment with ACTH or Cortisone.*

PERIOD	NO. OF CASES
Disappeared within 1 to 7 days	24
Disappeared within 8 to 14 days	9
Disappeared after 14 days	1
Disappeared during treatment, but time of disappearance not reported	20
Either appeared for 1st time during treatment or failed to disappear during treatment	4
Persisted until patient's death	6
Total	64†

*Time for disappearance was usually based on disappearance of a pericardial friction rub.

†These 64 cases were reported by 18 groups of investigators.[4-6, 11, 18-21, 24, 27, 29, 30, 35, 38, 40, 43, 44, 46, 49]

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Prolongation of PR interval in the electrocardiogram. An abnormally long atrioventricular conduction time as measured by a prolonged PR interval in the electrocardiogram of children and young adults with rheumatic fever is generally accepted as being due to active rheumatic carditis. Rarely, such a finding may persist for many months or years after all other signs of active rheumatic fever have disappeared. In the vast majority of cases the PR interval shortens to within normal limits along with the subsidence of other signs of active disease. Therefore, changes in the PR interval in patients being treated with cortisone or ACTH may give some indication whether therapy is suppressing the inflammatory process in the heart.

Information of this kind is furnished in 9 of the articles that have been reviewed. The findings reported in each of these 9 articles are briefly summarized.

Harris et al.[29] observed that a markedly prolonged PR interval in 1 patient became rapidly shorter with cortisone therapy so that it was within the normal range on the third day of treatment. After discontinuation of therapy there was an exacerbation of the rheumatic process, and with this the PR interval again became long.

In 5 of 7 patients with prolongation of the PR interval described by Barnes et al.[4] the abnormality disappeared within seven or eight days of hormone treatment.

Prolongation of the PR interval "showed a definite and consistent change to normal" in only 3 of 10 patients with this abnormality in the series of ACTH-treated cases reported by Dorfman et al.[30] In 4 others there were questionable changes.

The PR interval was considered to be definitely abnormal in 13 patients observed by Johnson and his associates,[46] and in all it shortened to normal limits during treatment with cortisone or ACTH.

In 2 cases of chronic rheumatic fever and an abnormally long PR interval reported by Young and Rodstein,[38] 1 patient, who received ACTH, showed a shortening of the interval to well within normal limits. There was no change in the other patients during three weeks of cortisone therapy.

Bywaters and Dixon[40] noted shortening of the PR interval during five days of ACTH administration in a patient in whom this interval was 0.40 second before therapy. In another patient a PR interval of 0.22 second failed to change during eight days of ACTH treatment.

Electrocardiographic changes, including prolongation of the PR interval, reverted to normal during ACTH therapy in all of 12 patients observed by Kelley.[20] The time required was twenty-six days in 1 but only three to thirteen days in the other 11.

Griffith and his associates[22,23] similarly noted a reversion to normal of electrocardiographic abnormalities that were present in 6 of their hormone-treated patients. The abnormalities varied from "prolonged PR interval to third degree heart block."

Prolongation of the PR interval was said to be present in 14 of 30 young adults with rheumatic fever whom Shopfner and Seife[45] treated with ACTH. In 1 patient the abnormality disappeared before therapy was started. One of the remaining 13 patients (this was the only fatal case in their series) continued to have an abnormally long PR interval. In all the others the conduction time returned to normal limits—within four to eleven days in 9 and within twenty-six to sixty-five days in 3 patients.

It is evident from the observations summarized here that of a total of 66 patients reported to have a prolonged PR interval 54, or 82 per cent, showed a reversion to normal during therapy with ACTH or cortisone, although in a few cases abnormality of conduction again developed after the discontinuation of treatment.

From these data alone it is not possible, of course, to determine whether the abnormality of the PR interval would have disappeared in such a large proportion of the patients if they had not been treated with hormones; consequently, final conclusions are not justified. Nevertheless, the incidence figure of 82 per cent is impressive and adds to the weight of evidence suggesting that cortisone and ACTH suppress the rheumatic inflammatory process in the myocardium.

Congestive heart failure. In patients with rheumatic fever and rheumatic heart disease congestive heart failure can be caused by weakening of the heart muscle from the rheumatic inflammatory process (rheumatic myocarditis), excess strain placed on the heart muscle by damaged and mechanically inefficient valves and irreversible changes in the heart muscle secondary to rheumatic inflammation. Often, all three factors combine to bring about the development of congestive heart failure, but in any given case any one of the factors may be the most important.

Failure developing early in an initial attack of rheumatic fever is usually due to weakening of the myocardium from the acute inflammatory process. When it develops late in an initial attack or during a recurrence of rheumatic fever, mechanically damaged valves and a heart muscle weakened by irreversible changes are probably important causes, but the superimposed rheumatic inflammatory process may also contribute.

Although rheumatic carditis is only one of three possible factors responsible for congestive heart failure, when failure and active rheumatic fever are both present and when lessening or subsidence of the signs of active rheumatic fever are accompanied by disappearance of the signs of failure, it seems reasonable to conclude that the active rheumatic process in the heart must have been playing an important part in the production of the failure. Similar conclusions

seem justified when anticongestive measures that fail to control heart failure during active rheumatic fever bring about satisfactory control as the signs of active rheumatic fever lessen or subside.

It also follows that, when congestive heart failure accompanies active rheumatic fever, spontaneous improvement in the heart failure or control of the heart failure by previously ineffective anticongestive measures is an indication that the active rheumatic carditis is lessening.

Because of the correlation that frequently exists between improvement in active rheumatic carditis and improvement in congestive heart failure, it is important that consideration be given to the observations that have been reported regarding the course of failure in patients with rheumatic fever treated with cortisone or ACTH. Of the various articles in the medical literature that were reviewed in the preparation of this article, 12 furnished information of some kind concerning congestive heart failure in patients who were given hormone therapy. The pertinent findings reported are summarized below; the articles are considered in chronologic order.

Massell and his associates[5,6] observed congestive heart failure in 6 patients with rheumatic fever. In 3 of these the signs of congestion disappeared completely during treatment with ACTH. In a fourth the signs, which before therapy had included an enlarged, tender liver, cough and orthopnea, lessened to such an extent that three weeks after the beginning of hormone treatment the only residual sign was a liver edge palpable just slightly below the right costal margin. Furthermore, administration of a mercurial diuretic, which had previously been required, was omitted two weeks later without the development of any increase in the signs of congestion. The remaining 2 patients in whom failure persisted throughout hormone therapy had chronic rheumatic fever and severe long-standing heart disease, 1 of six months' duration and the other of at least three or four months' duration.

Three of 4 cortisone-treated patients described by Harris et al.[29] had congestive heart failure. In 2 of these the signs of failure first appeared four to ten days after treatment had been started, but in both patients the congestion was controlled by "the usual therapeutic measures." The third patient already had signs of failure, including a large liver, by the time cortisone was started, and these signs disappeared within three weeks of hormone treatment.

Congestive heart failure was present in 13 patients of the series presented by Dorfman et al.[30] In 3 patients this condition was accentuated during ACTH therapy, but could be controlled by mercurial diuretics or withdrawal of the hormone for brief periods. In 10 of the 13 patients, however, evidence of failure had disappeared before the cessation of ACTH. No patient in this group had a recurrence of failure after therapy.

Rathbun, McAlpine and Manning[19] reported a case of acute rheumatic fever in which congestive heart failure developed during a two-week period of salicylate therapy. These signs subsided during treatment with cortisone.

Bunim and his associates[35,36] observed that failure associated with rheumatic fever disappeared in 5 of 8 children without the use of any anticongestive measures. In 2 of the other 3 patients failure was apparently controlled by diuretics and digitalis.

Signs of congestive heart failure were described in 3 patients studied by Chamberlain, Hay and Freeman.[43] One of these patients, who was suffering from severe rheumatic fever and carditis, was treated with only small amounts of cortisone. In spite of this therapy the failure persisted until the patient died twenty-three days later. In a second patient signs of fluid retention developed on the eighth day of cortisone therapy, and, therefore, the hormone treatment was discontinued. Mercurial diuretics were not administered until after discontinuation of the cortisone. A third patient manifested congestive heart failure while being treated with salicylates, and this condition became worse after the therapy was changed to cortisone. However, the situation was controlled by mercurial diuretics, and apparently all signs of failure had disappeared by the end of the second week of cortisone treatment.

Two patients treated with cortisone by Boone and Beach[44] apparently continued to have failure and died, 1 on the ninth day of therapy and the other on the tenth day. One of the patients, who was treated during a recurrence of rheumatic fever, was given only 38 mg. of the hormone a day along with a salicylate. The other was given somewhat larger doses but he had already been ill for some time with chronic heart failure by the time treatment was begun.

Young and Rodstein[38] found that congestive heart failure that had been refractory to all other measures cleared entirely in 4 of 5 patients treated with cortisone or ACTH. These investigators considered the effect of the hormones to be quite striking. Although during the early phase of treatment the maintenance of a low-sodium diet and the frequent use of mercurial diuretics were necessary, once regression of the failure became definitely established, the administration of mercurial diuretics was no longer required, and, after the evidence of failure had disappeared, the restricted diet was also no longer necessary.

Bach, Freedman and Bernstock[21] included 2 patients with congestive heart failure among those treated with cortisone. In 1 of these fluid retention apparently developed a week after hormone therapy had been started. It again disappeared with the administration of a mercurial diuretic. When cortisone was finally discontinued, the patient remained free of signs of heart failure. The second patient already had fairly marked signs of failure by the time cortisone was started. The congestion could be controlled dur-

ing hormone treatment with mercurial diuretics, and, after the course of hormone therapy had been completed, the patient continued to get along well without any return of the signs of congestion.

Kearney and Murray[48] briefly reported a patient with "typical rheumatic fever" and congestive heart failure who did not respond to digitalis, oxygen or Mercuhydrin but who showed a "dramatic response" when treated with cortisone. A rapid response to treatment with cortisone or ACTH was also observed in some of the patients with rheumatic fever treated by Brochner-Mortensen.[13]

Rowe, McKelvey and Keith[50] reported that congestive heart failure was present in 6 of 26 patients who received either cortisone or ACTH therapy. Although these authors stated that "in all but 1 case the failure was adequately controlled by diuretics, low-sodium diet, and Digoxin therapy" and that "in no case did the degree of congestive failure markedly worsen under treatment with hormones" it is not clear from their article whether the heart failure actually improved during or after the administration of the hormones.

Ten of the 12 reports that have been reviewed here supply sufficiently detailed information to allow for a tabulation of the data regarding the course of congestive heart failure. Such a tabulation reveals a total of 40 patients with failure when cortisone or ACTH therapy was begun and disappearance of signs of failure during hormone therapy in 27 of these patients. In 3 additional patients the congestion lessened. Thus, definite improvement occurred in 30 patients—75 per cent.

For the reasons discussed above, this improvement in congestive heart failure during hormone therapy suggests that the active rheumatic inflammatory process in the heart (carditis) must have subsided or lessened in the 30 patients in whom the changes were observed. Since one of the physiologic effects of cortisone and ACTH is a retention of sodium and water, which in itself tends to aggravate congestive heart failure, it is difficult to avoid the conclusion that lessening of the rheumatic inflammatory process in these 30 patients caused sufficient improvement in myocardial function to overcome the fluid-retaining effect of the hormones.

That congestive heart failure did not improve in all 40 patients is not surprising when consideration is given to the fact, previously pointed out, that active rheumatic inflammation of the heart is only one of three factors that contribute to the production of heart failure, the other two being valvular damage and irreversible myocardial changes. In fact, since rheumatic fever of long duration and previous attacks of rheumatic fever provided ample opportunity for the development of permanent valvular and myocardial changes in many of the 40 patients with failure, the figure of 75 per cent for the incidence of improvement is actually quite impressive.

Histopathologic Observations

The medical literature covered by this review contains a limited number of reports concerning the morphologic appearance of tissues obtained from patients with rheumatic fever treated with cortisone or ACTH. In 4 cases the tissues consisted of biopsied subcutaneous nodules; in 15 cases the tissues were obtained at autopsy. The pathological findings, which were described in considerable detail in some cases, were only briefly mentioned in others.

Bunim[33] compared the microscopical picture of a nodule removed before treatment from a boy during the sixth week of his first attack of rheumatic fever with that of a small residual nodule removed from the same patient after thirty-eight days of hormone therapy (three days of ACTH followed by thirty-five days of cortisone). The microscopical section of the nodule that was first biopsied showed areas of inflammation characterized by dense infiltration with many pleomorphic mononuclear cells and some multinuclear cells, which were aggregated about foci of fibrinoid material and by the formation of new small blood vessels. In the nodule removed after hormone treatment the fibrinoid material was still present, but the small blood vessels and the cellular infiltration that characterized the inflammatory reaction were no longer visible. Bunim considered the difference in appearance of the sections of these two nodules to be quite striking.

In a nodule biopsied after three weeks of hormone therapy Keith and Neill[49] also observed microscopical evidence of healing.

On the other hand Johnson et al.[46] and Bywaters and Dixon[40] found no difference in the histologic appearance of nodules removed before and after treatment with hormones. In the case reported by Johnson and his co-workers the patient was treated with ACTH for twenty days before the second nodule was removed, but the dose of the hormone was not stated. In the case presented by Bywaters and Dixon the second nodule was removed after only eight days of treatment with ACTH—a period that may well have been too short for recognizable changes to have become apparent.

The 15 autopsied cases can be divided into two groups, one consisting of 3 cases in which the histologic findings suggested that there had been some suppression of the rheumatic inflammatory process by the hormones and the other consisting of 12 cases in which the findings were characteristic of rheumatic inflammation observed in fatal cases of rheumatic carditis not treated with hormones.

The first of the 3 patients with some evidence of suppression was a boy with chronic rheumatic fever, severe rheumatic heart disease and congestive heart failure described by Massell and Warren.[8] Although he had been treated with ACTH for over eleven weeks and had received sufficient hormone therapy to cause fairly marked Cushing facies, the dose of

ACTH had been reduced to very small daily amounts for at least three or four weeks before a rapidly fatal bilateral jugular thrombophlebitis developed. Microscopical examination of the myocardium and endocardium revealed areas consistent with a subacute or healing process, but Aschoff bodies were not observed and fibrinoid changes were minimal.

The second case, in a girl with a long-standing history of rheumatic fever, severe rheumatic heart disease and congestive heart failure, was reported by Young and Rodstein.[38] She was treated for thirty-five days with a total of 3920 mg. of cortisone (average of 112 mg. a day) before she finally died. Postmortem examination revealed certain abnormal findings, but these were interpreted as characteristic of healed or healing rheumatic lesions. Microscopical evidence of active rheumatic carditis was absent.

The third case, reported by Golden and Hurst,[69] was in a girl who had had rheumatic fever for at least four months before her final course of hormone therapy. Early in her illness she had responded to thirty days of treatment with small to moderate doses of ACTH and cortisone, but after being without hormones for six weeks she had a fatal relapse. Before she died she received 100 mg. of cortisone a day for four days by mouth and then 300 mg. of cortisone a day for an additional ten days intramuscularly (total of fourteen days of cortisone therapy). At autopsy there were some lesions interpreted as long-standing healing lesions, and these did not appear to differ significantly from those seen in rheumatic carditis not treated with ACTH or cortisone. However, there also were acute lesions that had an atypical appearance in that they showed remarkably little or no cellular reaction. Large, mononuclear Aschoff cells were completely absent. Golden and Hurst interpreted the lesions as representing a "suppression of cellular reaction to altered collagen."

The 12 remaining cases comprising the second group were reported by Rosenblum,[70] Smith,[71] Spain and Roth,[72] Dorfman et al.[30] (4 cases), Chamberlain, Hay and Freeman[43] (2 cases), Boone and Beach,[44] Shopfner and Seife,[73] and Rowe, McKelvey and Keith.[50] The microscopical sections in all these cases were said to be characteristic of active rheumatic carditis.

The findings in these cases indicate that the rheumatic inflammatory process had not been suppressed by the hormones that had been administered before the fatal outcome. Although it is difficult to reject this interpretation for these particular cases a careful review of the facts raises some question about the reliability of applying this interpretation to hormone-treated patients with rheumatic fever in general. These facts are as follows:

All the patients had had either long-standing rheumatic fever and rheumatic heart disease or previous rheumatic fever with cardiac involvement before the final course of therapy with cortisone or ACTH.

On the basis of present knowledge either the dose of the hormones was entirely too small to cause an appreciable degree of suppression of the rheumatic inflammatory process or the period of treatment before death was too short. Thus, 1 patient received cortisone for only thirty-six hours before death, 3 received ACTH for four or five days, and 2 received ACTH for only seven days. In 1 case, reported by Boone and Beach,[44] the patient was treated with cortisone for as long as thirteen days, but the dose was only 100 mg. a day. Another patient was treated for six weeks, but subsequently there was a relapse and two weeks elapsed between the last dose of cortisone and the death of the patient.

The only patient in the entire second group of 12 fatal cases who received treatment that could be said to be at all adequate in terms of present standards was described by Shopfner and Seife.[73] This was a nineteen-year-old boy who was started on moderate doses of ACTH ten days after the onset of a second attack of acute rheumatic fever. Hormone therapy was continued for four weeks, but then, when it was discontinued because of marked Cushing facies, the patient became very much worse, dying four days later. Autopsy revealed hemorrhagic pneumonia (presumably rheumatic) and active rheumatic myocarditis and valvulitis though no definite Aschoff bodies could be demonstrated.

In conclusion it seems that the available histologic data do not throw much light on the question of whether cortisone or ACTH can suppress the rheumatic inflammatory process. The few reports regarding the appearance of biopsied nodules are contradictory. The autopsy data are also contradictory. Although the majority of autopsied cases failed to give evidence of healing of the rheumatic lesions, most of these patients had been treated with only very small doses of hormones or they died so soon after the beginning of treatment that there was not sufficient time for the hormones to bring about appreciable changes in the cardiac lesions.

Finally, it should be pointed out that autopsy studies automatically select patients who do not do well; they provide no information about patients who respond to treatment.

Summary of Evidence Regarding Suppression of Carditis

The extremely limited and contradictory histologic data in the medical literature do not throw much light on the question of whether cortisone or ACTH can suppress the rheumatic inflammatory process. On the other hand information regarding the response of various clinical manifestations of rheumatic fever to hormone treatment, although by no means as com-

plete as desired, is sufficient to justify certain tentative conclusions regarding the suppressive effect of the hormones on the rheumatic inflammatory process responsible for these manifestations.

Fairly conclusive data are available to indicate that fever and the joint manifestations of rheumatic fever respond promptly and completely during treatment with cortisone and ACTH. In all probability subcutaneous nodules also disappear under the influence of the hormones provided that therapy is administered in sufficiently large doses and continued over a sufficiently long period. The responses of these three manifestations, in turn, indicate that the underlying inflammatory process responsible for them is completely or highly suppressed by cortisone and ACTH.

Practically all reports reveal that the elevated sedimentation rate that usually accompanies acute rheumatic fever almost invariably returns to normal limits during hormone therapy. Although there is some evidence that the hormones may directly influence the sedimentation rate by interfering with the production of certain plasma proteins it seems likely that such a direct effect is relatively minor and that the change in sedimentation rate is mediated largely by alteration on the severity of the rheumatic inflammatory process in the various tissues.

Data bearing on the problem of whether erythema marginatum is influenced by cortisone and ACTH are still meager and too inadequate to allow for any definite conclusions. Furthermore, although this manifestation is nearly always the result of rheumatic fever, its significance as a sign of rheumatic activity is still not fully understood. Therefore, the limited and contradictory observations that have been reported so far on the response of erythema marginatum cannot be accepted as evidence either in favor of or against a suppressive effect of the hormones on rheumatic inflammation.

More data are available regarding the course of chorea in patients with cortisone and ACTH, and, although they may be inadequate for final conclusions, they suggest that this condition actually is influenced favorably by the hormones. On the other hand chorea, like erythema marginatum, is a manifestation whose significance as a sign of rheumatic activity is not fully understood; therefore, the observations on the course of chorea, like those on the course of erythema marginatum, do not yet aid in solving the problem of determining whether cortisone or ACTH can suppress rheumatic inflammation.

The tissues involved in the production of joint pains and subcutaneous nodules are extracardiac, and, therefore, suppression of inflammation in these tissues by cortisone and ACTH does not necessarily indicate that the hormones also suppress carditis. Although inflammation in the heart may contribute to the production of fever and elevation of the sedimentation rate these two manifestations could be explained largely by rheumatic involvement of the extracardiac tissues. Hence, the favorable action of hormones on these manifestations does not necessarily indicate an effect of the hormones on the inflammatory process in the heart.

The manifestations that may be related directly to the inflammatory process in the heart (carditis) are gallop rhythm, tachycardia, pericarditis, prolongation of the PR interval in the electrocardiogram and congestive heart failure. These manifestations require special consideration.

Gallop rhythm frequently and tachycardia fairly often have been noted to subside during hormone therapy. Although these changes could be the result of lessening of the severity of rheumatic carditis the possible effect of suppression of fever in the subsidence of tachycardia and the possible influence of alterations in heart rate on gallop rhythm make it difficult to evaluate the significance of changes that occur in these two manifestations during treatment with hormones. On the other hand the favorable effects of hormone therapy on pericarditis, prolongation of the PR interval and congestive heart failure are not open to such question. The frequency with which the last three manifestations have been observed to lessen and to disappear is striking and strongly suggests that active carditis is actually suppressed by cortisone and ACTH.

Additional indirect evidence that the hormones suppress carditis is offered by the observations of their effect on subcutaneous nodules, even though the subcutaneous nodule is an extracardiac lesion. As pointed out previously[10] the subcutaneous nodule is a significant manifestation because only rarely does a patient with rheumatic fever and nodules escape heart damage, and because the microscopical architecture of the subcutaneous nodule resembles in many respects that of the cardiac lesions of rheumatic fever. Hence, it seems not unreasonable to infer that treatment that favorably affects rheumatic subcutaneous nodules will similarly affect the rheumatic lesions in the heart.

In summary, then, although final conclusions are not justified, the available data strongly suggest that the manifestations of carditis as well as the extracardiac manifestations of rheumatic fever are frequently influenced favorably by cortisone and ACTH. These data, in turn, suggest that the rheumatic inflammatory process responsible for these manifestations can be suppressed by the hormones.

Effect of Hormone Therapy on Duration of Rheumatic Fever

The ideal therapeutic agent for rheumatic fever would be one that not only suppresses rheumatic inflammation but also eradicates the underlying process so that, when treatment is finally discontinued, signs of rheumatic inflammation do not reappear. Therefore, in evaluating the usefulness of cortisone and corticotropin, one should know the answer to the question, Can cortisone or ACTH shorten the duration of an attack of rheumatic fever?

The opinions of investigators regarding the answer to this question, as well as other important questions concerning the therapeutic value of hormones, vary considerably. Some of these opinions are reviewed. Before this is done, consideration is given to the so-called rebound phenomenon, which has an important bearing on the problem of estimating the duration of an attack of rheumatic fever.

From the observations already discussed in the previous section, it is evident that in many patients the various clinical and laboratory signs of rheumatic fever subside during treatment with ACTH or cortisone. After such a response some patients remain free of all signs of rheumatic activity even though the hormones are subsequently reduced in dosage or discontinued. On the other hand, in some cases, when the dose of the hormones is reduced to a low level or when treatment is discontinued, fever, elevation of the sedimentation rate and other manifestations of rheumatic fever reappear and continue for many weeks or months. In a third and sizable group of patients, when the dose of the hormones is reduced or when therapy is discontinued, there is a relapse of rheumatic manifestations, but after a few days to a week these manifestations begin to subside spontaneously and soon disappear completely even though no further therapy is given.

Most physicians who have studied the use of cortisone or ACTH in rheumatic fever have encountered the rebound phenomenon, but the frequency with which it has been observed has varied. Some investigators believe that the frequency of these rebounds can be lessened by prolongation of the period of therapy or by very gradual tapering of the dose of the hormones before treatment is discontinued.

In cases in which rheumatic manifestations have continued for a long period after the appearance of a relapse there seems to be no question about the interpretation that before the relapse hormone therapy had suppressed but had not eradicated the rheumatic process and that in all probability the total duration of the attack had not been shortened.

On the other hand the temporary relapse, for which the term rebound is especially appropriate, is not so readily open to interpretation. Since the rebound is characterized by the reappearance of manifestations of rheumatic fever and therefore is presumably due to the reappearance of rheumatic activity, it might be concluded that the rheumatic process had been continuing throughout the period of therapy and that the time in which the rebound subsided was the same as that in which the manifestations of rheumatic fever would have subsided if hormone therapy had not been given. It is also possible, however, even though the end of the rebound is accepted as the end of the rheumatic episode, that the total duration of the illness was less than it would have been if hormone therapy had not been used.

With this brief discussion of the rebound phenomenon and its possible interpretations as a background, the opinions of various investigators regarding the effect of cortisone and ACTH on the duration of rheumatic fever are reviewed.

Wilson and her associates[15,16] are apparently the only investigators who believe unequivocally that hormone therapy can actually shorten the duration of an attack of rheumatic fever. They observed that the early treatment of the disease with a relatively short course of ACTH (usually for about a week) was "followed by the arrest and termination of active carditis" so that all 24 patients who received adequate therapy were ambulatory one to three weeks after therapy had been discontinued. However, it is to be noted that these physicians distinguish between signs of carditis and other manifestations of rheumatic fever and that they do not seem to attach much significance to the presence of the latter in many of their patients after completion of the short course of hormone treatment. Thus, some of their patients had arthritis, fever or nodules after ACTH had been discontinued,[15] and the "sedimentation rate remained elevated for weeks in the majority of patients."[16]

A view entirely opposite to that of Wilson et al. has been expressed by Bunim and his associates,[35,36] Kearney and Murray,[48] and Hench and his co-workers at the Mayo Clinic.[4,74] The Mayo Clinic group, who were responsible for first noting and describing the apparent therapeutic value of cortisone and ACTH in rheumatic fever, observed that the hormones suppressed the acute manifestations of the disease as long as adequate administration was continued, but that in the majority of their cases one or many manifestations of the acute rheumatic state recurred as soon as administration of the hormones was discontinued or when inadequate doses were used.[4] Because of this high incidence of relapse they concluded that the hormones do not cure or shorten the course of rheumatic fever.[74]

Views that fall somewhat in between these two extremes have been expressed by others.

Massell and his associates[5-9] observed rebounds in a number of their patients when the dose of hormones was reduced to a low level or when therapy was discontinued, but they were impressed by the relatively short duration of these rebounds in many cases and by their frequent spontaneous subsidence. These investigators gained the impression, even after taking the rebound into consideration, that the duration of the rheumatic process in some of their hormone-treated patients was less than it would have been without therapy. On the other hand they emphasized the fact that this was only an impression and pointed out the following fact:

> . . . The well known variability of rheumatic fever even when it is uninfluenced by therapy, the variable course of the disease in the patients treated with pituitary adrenocorticotropic hormone and the relatively small number of patients so treated necessitate postponement of final judgment until there has been an opportunity to observe the effect of the hormone on a large number of patients with

rheumatic fever and to compare the clinical course of those patients with that of an adequate group of controls.[8]

Dorfman et al.[30] were similarly impressed by the favorable course of the disease in some of the patients whom they treated with ACTH but likewise emphasized the difficulty of determining whether hormone therapy changed the natural history of rheumatic fever and pointed to the need of studying a larger number of patients. Although transient rebounds were observed in many of their patients they considered it striking that congestive heart failure was not one of the manifestations to recur even though 13 patients in this series had had failure before therapy. Because of these observations they considered the possibility that therapy interrupted the activity of the disease in some cases, but they also considered the possibility that spontaneous subsidence of rheumatic activity was the explanation of the observed improvement.

The clinical course in 2 very ill patients with chronic rheumatic fever was interpreted by Young and Rodstein[38] as an indication that the rheumatic process had been terminated by therapy, but in 5 other similar patients the total duration of the disease did not appear to be shortened.

In one communication Griffith and his associates[22] concluded that the course of rheumatic fever is definitely shortened by hormone therapy, but in a second paper they[23] said the hormones must be considered to be "suppressive rather than curative."

Clinical observations suggested to Kelley et al.[20] that the fundamental pathology of rheumatic fever may be influenced and that the duration of the active phase of the disease may be shortened by treatment with hormones. However, they later noted that elevated levels of serum mucoprotein often persist in spite of clinical response, and they considered these findings to indicate possibly that disease activity also persists and that hormone therapy, therefore, may only be suppressive.[75]

From the various papers reviewed here it is difficult to avoid the conclusion that so far the weight of evidence favors the view expressed by Barnes and Hench that cortisone and ACTH are highly suppressive of rheumatic inflammation but that they do not actually halt or shorten the duration of the underlying pathologic process. However, the words "so far" should be emphasized, for, in fact, the available data are still inadequate to allow for final conclusions. The possibility that the hormones in some way influence the duration of rheumatic fever should not be dismissed, and further studies concerning this problem are needed. Such studies should be controlled and should include observations on patients treated with highly suppressive doses of the hormones over fairly long periods as well as on patients treated with large doses for only a few weeks or less.

(To be concluded)

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MEDICAL INTELLIGENCE

DIABETES MELLITUS FOLLOWING ACUTE PANCREATIC NECROSIS*

Report of a Case

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ACUTE pancreatic necrosis is a rare cause of diabetes mellitus. Detailed clinical and post-mortem studies of a patient who survived such a necrosis for a month are the basis for the following report.

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Case Report

J.A., a 38-year-old single Army private was admitted to the hospital on September 10, 1943, for continued treatment of a schizophrenic reaction, paranoid type.

Routine physical examinations were within normal limits until November 6, 1950, when prostatic hypertrophy and urinary retention were found.

A transurethral resection was done on December 12. When the diagnosis of adenocarcinoma of the prostate was made diethylstilbestrol administration was begun. Within the next 7 weeks the patient had a bilateral orchiectomy and implantation of radon seeds in the prostatic fossa. Clinical, biochemical and roentgenologic studies, as well as 7 interval cystoscopic examinations, during the following 2 years showed no abnormalities.

A routine cystoscopic examination on December 29, 1952, revealed moderate projection of the posterior wall of the urinary bladder near the trigone on the right. This was correlated with a palpable rectal mass and was thought to be a recurrence of the prostatic carcinoma. The blood pressure was 140/80. No additional treatment was recommended.

An acid phosphatase determination on March 30, 1953, was normal.

On April 3 the patient was examined because of edema of the legs and face. He weighed 106 kg. The blood pressure was 200/110. The irregularly enlarged mass was still present on digital examination of the rectum. The clinical diagnoses were recurrence of the adenocarcinoma of the prostate and edema from sodium and water retention. The

diethylstilbestrol was discontinued. A low-sodium diet was begun. Urinalysis on April 6 was normal. After 6 days of observation small doses of mercurial diuretics were given. There was a dramatic loss of fluid, and by April 20 the weight was 94 kg. On April 21 he seemed to be in pain, but his mental condition did not permit a history to be taken. On physical examination he appeared uncomfortable when pressure was applied to the epigastrium. Increased thirst was observed.

By April 24 he was listless, apathetic, drowsy, dehydrated and breathing heavily. The temperature was 101°F. by rectum, the pulse 120, and the respirations 32. The blood pressure was 100/80. The eyeballs were questionably soft, but there was no unusual odor to the breath. There were no findings suggestive of infection.

A qualitative test for sugar in the urine was strongly positive. (Twenty-nine previous urinalyses during hospitalization had been negative for sugar.) The blood sugar was 800 mg. per 100 cc. An electrocardiogram showed only sinus tachycardia. Energetic treatment with intravenous infusions of fluids, insulin, potassium chloride and penicillin was begun. During the first 8 hours of treatment 250 units of regular insulin was given, and, by the following morning, the blood sugar had dropped to 228 mg. per 100 cc. The serum chloride at that time was 120 milliequiv. per liter (normal 95 to 105 milliequiv.).

The patient emerged slowly from a semistuporous state; on April 26 he was placed on a liquid diabetic diet, and the insulin dosage regulated by urine color tests and blood sugar determinations. An electrocardiogram on April 26 demonstrated pronounced T-wave inversions. On April 27 he passed a foul, pasty stool. A serum amylase determination on that day was normal. By May 1 he was taking feedings fairly well, and the systolic blood pressure had reached 140. The penicillin was reduced and finally discontinued on May 4 after 6 days of normal temperature.

A lumbar puncture was done on May 6. Except for an elevated sugar the cerebrospinal fluid was normal. After a transient episode of cyanosis on May 7 medium moist rales were heard throughout the lower thirds of both lung fields. Additional findings at that time included questionable epigastric tenderness and bright-yellow feces in the rectum.

On May 21, after an episode of hematuria and several days of increasing weakness and profuse, yellow bowel movements not controlled by symptomatic treatment, the patient became cyanotic, and breathing became labored. In spite of oxygen and supportive treatment, he died at 8:25 a.m.

From May 3 until death on May 21 the temperature had been normal. Urinalyses before feedings had shown little or no sugar, and the blood sugar had remained within normal limits on daily totals of 70 to 95 units of regular insulin. The nonprotein nitrogen had not exceeded 55 mg. per 100 cc. The blood calcium and phosphorus on May 14 were 7.29 and 2.2 mg. per 100 cc. The T-wave inversions had disappeared by May 1, and the electrocardiogram was then normal except for a slightly prolonged QT interval. A roentgenologic bone survey 9 days before death disclosed no osseous metastases.

A complete autopsy was performed. There was gross and microscopical evidence of an acute necrosis involving the body and tail of the pancreas. The peripancreatic tissues exhibited fat necrosis. The adenocarcinoma of the prostate was continuous with a large tumor mass in the pelvis. Distant metastases were found in the liver, adrenal glands, spleen, right lung and right hilar lymph nodes. There was bilateral adrenocortical hypertrophy.

Discussion

Although acute pancreatitis is a cause of diabetes mellitus there are few detailed reports in the American literature of the metabolic sequelae of necrosis. The high mortality in acute pancreatic necrosis prevents the development of a significant number of cases of diabetes mellitus. Since unrecognized acute pancreatitis may account for abdominal pain in diabetic acidosis the possibility of pancreatitis or pancreatic necrosis should be considered in every case.

Warren et al.,[1] in an article on acute pancreatitis and diabetes, described in detail 5 cases. In 2 of these, at post-mortem examination, there was evidence of extensive pancreatic necrosis. The authors believed that diabetes mellitus was a complication of severe pancreatitis characterized by extensive hemorrhagic necrosis.

de Takats and Mackenzie,[2] discussing 30 cases of acute pancreatic necrosis, reported the development of diabetes in 2 patients known to have been sugar free before the acute necrosis.

Polayes et al.[3] presented a case of acute hemorrhagic pancreatic necrosis with sequestration and recovery. When last seen nine months after the original admission their patient was on a full diet and 15 units of insulin daily. Review of the literature revealed a similar case of pancreatic necrosis with slough and recovery; other cases of slough of the entire organ had been reported, but none of the patients had recovered.

Many of the earlier studies were done before the routine use of present-day biochemical methods. However, in 1948 Gambill and his co-workers[4] reported in detail a case of acute hemorrhagic pancreatitis with a disseminated fat necrosis, hypocalcemia, hypopotassemia, uremia, diabetes mellitus, ascites and bilateral hydrothorax. Their patient survived for seventeen days.

Acute pancreatitis is associated with a high incidence of biliary-tract disease. de Takats and Mackenzie[2] reported 81.2 per cent of biliary infection as the primary cause. In both fatal cases discussed by Warren et al.[1] there were multiple biliary calculi. The patient of Gambill and his associates[4] had more than 100 small, faceted stones. However, in the case presented above, the gall bladder was free of stones, and careful examination of the bile ducts revealed no calculi or other disease.

In addition to alterations in glucose metabolism in acute pancreatitis there are changes in the blood calcium. These changes, described by Gambill and his co-workers,[4] were also present in this case, in which the serum calcium was 7.29 mg. per 100 cc. (normal 9 to 11 mg.). The authors also noted that when the serum calcium fell below 7 mg. per 100 cc. the patient almost always died.

Although this patient's terminal course appeared to be consistent with an acute pancreatic necrosis the carcinoma of the prostate and adrenal changes deserve comment.

The carcinoma of the prostate, discovered twenty-nine months before death, had apparently been controlled by radon-seed implantation, orchiectomy and estrogen therapy. Careful follow-up studies, with frequent determinations of the acid and alkaline phosphatase and roentgenologic bone surveys, had shown no suggestions of metastases although local recurrence was evident on cystoscopic study five months before death. On post-mortem examination the soft-tissue metastases were extensive. No metastatic involvement

was apparent in the gall bladder or about the bile ducts. Death, hastened by the pancreatic necrosis and diabetes, would have resulted eventually from the carcinoma.

Adrenal involvement in metastatic carcinoma of the prostate is apparently uncommon. Mintz and Smith,[5] in a report on the autopsy findings in 100 cases of prostatic cancer, found adrenal involvement in 1 case in which the metastases were widespread.

The adrenocortical hypertrophy may have had one or more causes. Neoplastic emboli were found in the cortical capillaries. Of the causes of adrenocortical hypertrophy listed by Soffer[6] estrogen treatment, castration, insulin, shock and anoxia were all present at one time or another in this patient. The clinical picture before the onset of the acute pancreatic necrosis resembled in many respects a Cushing's syndrome, and the possibility of fatty pancreatic necrosis from such a syndrome cannot be ruled out.

Because androgens are believed to be an activating factor in the growth of prostatic cancer total adrenalectomy has been suggested as a treatment for prostatic carcinoma reactivated in spite of orchiectomy and continuous estrogen therapy. This procedure, not considered in the treatment of this patient, was recently discussed by Harrison, Thorn and Jenkins.[7]

Summary and Conclusions

A case of acute pancreatic necrosis producing diabetes mellitus is presented. Although a severe psychiatric illness prevented a history and accurate evaluation of physical findings a pancreatic accident was suspected clinically and confirmed by the subsequent course and post-mortem examination a month later. At autopsy a known, and probably unrelated, carcinoma of the prostate was found to have metastasized extensively. Explanations are offered for the adrenocortical hypertrophy noted at autopsy, and the possible etiologic relation of the adrenocortical change and the pancreatic necrosis is mentioned.

Acute pancreatitis and pancreatic necrosis should be considered as possible etiologic factors in diabetic acidosis, especially in the presence of abdominal pain.

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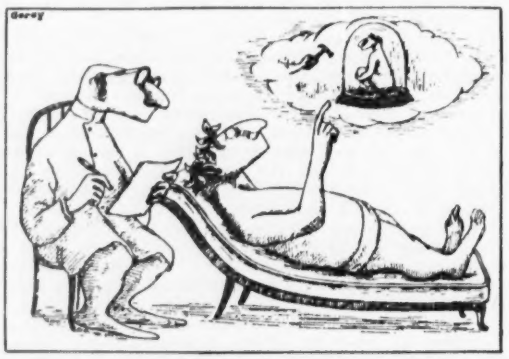
DOCTORS AFIELD

Merrill Moore

Joseph Garland, M.D.

Boston

Merrill Moore, psychiatrist, poet, philosopher and friend, was born on September 11, 1903, at Columbia, Tennessee. His background was one of letters and of language, for his father, John Trotwood Moore, a novelist and historian and also a poet, was one of the literary leaders of the South at the turn of the century. He became ultimately state librarian for Tennessee, a post to which Merrill's mother succeeded after the death of her husband in 1929. Raised in



Reproduced from the Collection, From a Psychiatrist's Notebook: A collection of American sonnets by Merrill Moore *(Christchurch, New Zealand: Pegasus Press, 1954), with the Permission of the Author.*

such an environment it was as natural for young Merrill to curl his fingers around a pencil as it was for the infant Hercules to strangle the serpents that invaded his cradle.

After attending public school Moore prepared for college at Montgomery Bell Academy in Nashville, then took his A.B. in 1924 and his M.D. in 1928 at Vanderbilt University. His interest in languages became apparent early, for he started learning French at nine, soon spoke and wrote it fluently and taught it at Fisk University in the summer of 1926. He studied Latin at Montgomery Bell, where he also gained a proficiency in Spanish that enabled him to read Cervantes in the original. Greek and German he acquired at Vanderbilt and was able to use the latter language competently on an undergraduate tour of Germany. It was at this time that he formed the habit of reading regularly in French, German and Spanish and somewhat irregularly in Sanskrit.

While at Vanderbilt he took also extracurricular instruction in Hebrew and Yiddish; it was not until

later, during his war years in the South Pacific, that he learned to converse in Maori, acquired a smattering of pidgin English and when in Shanghai scraped up a bowing acquaintance with Mandarin Chinese. Although currently reported to be investigating the somewhat abstruse nuances of Hittite, he has admitted defeat in every attempt to compose a sonnet in basic English.

So far as his more orthodox education and activities are concerned, Merrill turned north after an internship at St. Thomas Hospital, for training in psychiatry and neurology. This included a residency in neurology at the Boston City Hospital, the post of assistant physician to the Boston Psychopathic Hospital and a Commonwealth fellowship at the same institution from 1932 to 1935. From then on his professional career has been in psychiatry—mainly in private practice and at the Boston City Hospital and the Harvard Medical School, where he has been for several years an associate in psychiatry.

Moore's participation in World War II was largely in the Pacific, at first with the Thirty-ninth General Hospital—the Yale unit—in New Zealand, with special assignments in the general area. For his service to troops on Bougainville he was awarded the Bronze Star. After a tour of duty at Fort Devens as chief of the Neuropsychiatric Service he was sent to Nanking in January, 1946, as psychiatric consultant to Nanking Headquarters Command, remaining as surgeon to the Military Advisory Group in the service of Lieutenant General Albert C. Wedemeyer and later General George C. Marshall, on whose recommendation he received the Army Commendation Ribbon.

It is, however, his activities apart from medicine that qualify Merrill Moore as a "doctor afield"—activities also apart from his interest in conchology, his passion for taking pictures and his participation, for a number of years, in the annual 8-mile salt-water swimming marathon to Boston Light. For Merrill Moore is a poet of distinction—in total quality as well as supremely in total quantity, since he is probably the most prolific sonneteer the world has ever known. And withal there is gold in them thar hills; each rockerful of pay dirt contains its sparkling grains, and small nuggets of the pure metal come not infrequently to light.

This prolificity, with the irregularity of form and indifference to rhyme that accompanies it, might in a less instinctive writer of sonnets appear to be a serious fault, but it is an integral part of Moore's impatient genius even if through it his art is sometimes seen as through a glass darkly. His sonnets may, indeed, be likened to his own description of the raindrops that dance on exploding feet, in a sonnet that expresses the passion for water of this shell collector and salt-water marathon swimmer:

> I call it raining when it rains so hard
> That you are drenched if you walk in the rain
> Only a short while, are drenched to the skin
> Through clothes and shoes — there is no other word
> But raining to call that when the hard rain falls
> And soaks your hat; so that the water drips
> Off its brim across your nose and lips
> And chin, so that a stream of water falls
>
> From the roof, letting the gutters spout
> As water pell-mell leaps and hurries out
> To race down gutters — that should be called rain;
> That is rain and nothing else but rain,
> And unmistakable — striking the hard street —
> Small men dancing upon exploding feet.

Letters, words and poetry were so bred in the Moore bone that while still an undergraduate Merrill became the youngest member of the "Fugitive Group" of Nashville poets that met and read their verses and for four years published the poetry magazine *The Fugitive*.

It is one of this group, John Crowe Ransom, who wrote in 1929 the foreword to Merrill Moore's little book of "Fugitive Sonnets," republished last year in England, and gave possibly the best explanation of this natural genius.

> Merrill Moore is a spontaneous poet, that is, free and easy in his way of generating poems, beyond anybody I know . . .
>
> He has written many hundreds of poems. Some were written in shorthand, some on stray scraps of paper, and many have perished that were well worth preserving. For he has been the victim of his own facility in the following manner: he has scarcely been able to keep, copy and revise the old poem because it has always proved easier simply to write a new one.
>
> . . . . . .
>
> It is because Merrill Moore is an inevitable fountain of charming novelties that he has done what I doubt if any other living poet could do; and that is, publish himself fully, delicately, and beautifully in a book composed entirely of sonnets, or quasi-sonnets.

The many hundreds of poems have become many thousands, most of them sonnets, and they have appeared in nearly a dozen and a half volumes of various thicknesses, of which *M: One Thousand Autobiographical Sonnets*, published in 1938; *Clinical Sonnets; Illegitimate Sonnets; Case Records from a Sonnetorium*, and *More Clinical Sonnets*, all published between 1949 and 1953, are best known to the medical sonnet-reading public.

Despite their failure to observe Merrill Moore's brand new tradition of freedom and easiness in sonnet writing the following lines, penned painfully in formal fashion by one far less gifted, may nevertheless be appropriate to close this brief essay:

> Iambics five compose each tailored line
> Of the precise fourteen the rules allow —
> In rhyme, some form of standardized design
> Like the Petrarchan verse or like enow
> The style of Avon in the Bard's refrains.
> Such is the sonnet whereby Wordsworth found
> Brief solace in its animating strains,
> By thought and spatial limitations bound.
> Now a new rock is touched as with the stave
> Of a new Moses in a new found land
> And forth a torrent leaps of sonnets brave
> That shout defiance to the standard brand.
> No meager printer's em is this rich store —
> M stands for thousands, Merrill, Moore and more!

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40311

PRESENTATION OF CASE

A sixty-five-year-old saleswoman was admitted to the hospital because of an abdominal mass of several months' duration.

Fifteen years before admission there was the insidious onset of anorexia, occasional vomiting and weight loss not associated with diarrhea or melena. She had "felt something" in the right lower quadrant "for years." A diagnosis of appendicitis was made, and at operation an inflammatory mass that involved the cecum and appendix was removed along with those structures. After the operation she had diarrhea, with 4 to 6 loose, watery stools a day. These occurred after each meal and occasionally at night and were associated with some urgency. Her weight fell from 100 to 84 pounds. This pattern of diarrhea continued for the next fourteen years, until four months before admission, when the stools became formed. With this change, she noted bloating, discomfort in the lower abdomen and anorexia, with occasional vomiting when she tried to eat. She passed gas and formed stools every day and intermittently became less distended. Tenderness developed in the right lower quadrant, where she noted a lump that was painful on pressure or motion, with some extension to the periumbilical region. Because of the mass she was admitted to another hospital. An intravenous pyelogram and cholecystogram were normal. An upper gastrointestinal study and barium-enema examination, as interpreted here, showed a configuration of barium-filled bowel in the right lower quadrant that was thought to represent an ileocolostomy. On the colon side of the anastomosis there was a persistent, concave indentation like that caused by an extrinsic mass. Extending from this portion of the colon was an irregular, tubular sinus tract, measuring 5 cm. in length and 8 mm. in diameter, that appeared to have a blind ending. The portion of the ileum adjacent to the colon appeared to have a fixed position, which was semicircular; the proximal areas of small bowel appeared normal (Fig. 1 and 2). After these studies diarrhea returned. She was admitted to this hospital for treatment.

The past history revealed two episodes of ulceration on the leg after minor trauma that healed with antibiotics. There had been some urinary frequency without dysuria. The patient noted a "lump" in the throat and epigastric discomfort when she was discouraged and often cried with these symptoms. Her mother had died of diabetes.

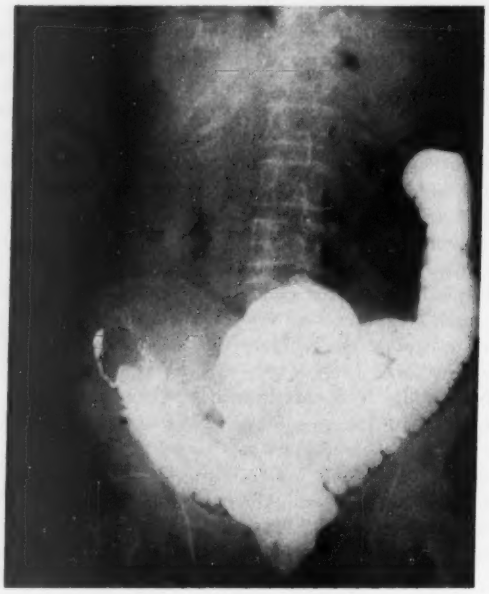


FIGURE 1. *Barium-Enema Examination. Arrow points to the fistulous tract.*

Physical examination showed a tired, thin woman with evidence of weight loss. The skin was dry, and the proximal and distal interphalangeal joints were enlarged. The heart and lungs were normal. The abdomen was tender, with a large, ill defined mass in the right lower quadrant. Spasm and guarding prevented more careful delineation. There was a well healed midline suprapubic scar. On rectal examination the right side was full and slightly tender.

The temperature was 99.2°F., the pulse 80, and the respirations 20. The blood pressure was 140 systolic, 70 diastolic.

Urinalysis demonstrated a + test for albumin and a negative test for sugar. Examination of the blood revealed a hemoglobin of 11.6 gm. per 100 cc. and a white-cell count of 10,100; the prothrombin time was 15 seconds (normal, 13 seconds). The nonprotein nitrogen was 17 mg., and the total protein 6.3 gm. per 100 cc. A plain film of the abdomen disclosed a small amount of residual barium in diverticula of the sig-

moid colon and an ill defined mass overlying the right innominate bone. There were no abnormal calcifications. Sigmoidoscopic examination was negative.

On the third hospital day an operation was performed.

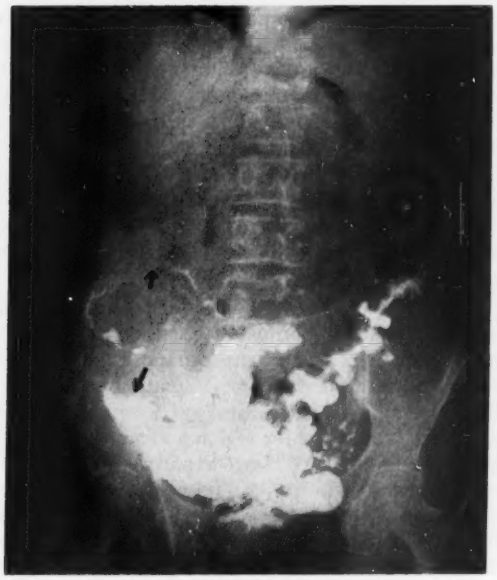


FIGURE 2. *Small-Bowel Examination.*
Lower arrow points to the compressed portion of the colon; upper arrow points to the displaced and fixed small-bowel loop.

DIFFERENTIAL DIAGNOSIS

DR. LELAND S. MCKITTRICK*: Dr. Gibbons, may I see the x-ray films? I cannot make any definite diagnosis from the history alone.

DR. JOHN F. GIBBONS: These films are from an outside hospital; therefore, I do not know what the fluoroscopist found. In trying to reconstruct what was going on, I think the colon has been filled, this being sigmoid loop, descending colon and low redundant transverse colon overlying the right side of the rectum. In the right lower quadrant there seems to be a blind loop of bowel, which is coated with barium, and a saucer-shaped indentation on the colon (Fig. 1). A film made after evacuation shows about the same findings. A tubular structure filled with barium extends also from the indented part of the colon. Later, on examination of the small intestine, the upper loops of small bowel look perfectly normal but, again, in the right lower quadrant of the abdomen there is a shallow indentation on a loop of bowel and a narrowed loop of what I assume to be small bowel and some residual barium in the fistulous tract seen on the barium-enema study. I think that there has been a previous ileocolostomy or else a fistula between the colon and ileum, with a blind tract extending laterally. There is a mass in all the films that can be seen pressing on this portion of the colon and may fix a loop of small bowel. After admission a survey film again demonstrates the abnormal density overlying the right innominate bone as described, which seems to be compressing a gas-filled loop of bowel and which I assume to be the distal or proximal portion of the redundant transverse colon.

DR. MCKITTRICK: Do these findings indicate that a segment of bowel was removed there?

DR. GIBBONS: I think one must assume that, because at no time do we see the ascending colon even though the proximal small bowel is well filled with barium and on the barium-enema studies only the colon is filled.

DR. MCKITTRICK: You cannot tell whether that is mucosa or not?

DR. GIBBONS: I think it is; it looks like swollen mucosa, but I cannot make out any more than that.

DR. MCKITTRICK: Can you tell whether there is ulceration or not?

DR. GIBBONS: I suspect that there may be an ulceration because there is an irregular pool of barium in the area where the sinus tract leaves the colon. If this is colon I think one has to assume that there is an ulceration with a fistula from it.

DR. MCKITTRICK: This sixty-five-year-old woman with a fifteen-year story presumably was operated on for an inflammatory lesion in relation to the cecum and appendix. It seems reasonable to assume that the transverse colon and terminal ileum had been anastomosed and the intervening segment of bowel removed. The important question is, What was the mass that was removed? One wonders why the diarrhea developed after the operation and persisted so long. Any patient who has had a colectomy on the right has diarrhea, which persists for varying periods but is transient and not significant. This patient, however, had 4 to 6 watery stools a day and occasionally at night. I think one need not pay too much attention to diarrhea in the daytime but diarrhea that occurs at night really has clinical significance. Urgency suggests a lesion that involves the lower large bowel. If she did have such a lesion, that might help a great deal in completing this picture. I do not think we shall know whether or not she had such a lesion because by the time of admission the diarrhea had let up and the normal sigmoidoscopic examination excluded a process in the lower large bowel.

Perhaps I should try to hazard a guess about the early lesion because, presumably, if one is to be logical one should try to relate that to the present condition. That seems to me to make better sense than it does to attempt to bring in two separate conditions. It does not seem to me that I need pay any attention to carcinoma as the primary lesion. Whether carcinoma must be considered at present is a different story.

Can we exclude a chronic appendiceal abscess as the primary lesion? The history was long for that,

*Consulting visiting surgeon, Massachusetts General Hospital.

and the subsequent course makes it reasonably easy for me to dismiss this as the original lesion.

I think one is compelled to think of lymphoma. The ileocecal region is a relatively common place for that. Incidentally, it seems to me that I saw many more lymphomas in that region in past years than I have seen recently. Again, the subsequent course seems to have eliminated that condition. If I cannot consider it now I do not think I should suggest that it was present at the time of the previous operation.

Whenever there is a mass or a sinus, internally or externally, one is compelled to think of a foreign body. I am unwilling for several reasons to make that diagnosis. I do not happen to have seen a foreign body in relation to a previous operation that remained in situ for fifteen years. I mention it because it must always be considered, but I am quite willing to leave that out of the picture.

Another condition that we infrequently see is actinomycosis. Again, I think the duration of the symptoms is somewhat against that diagnosis, but it must always be included in a discussion of lesions that involve the bowel, particularly when there is an inflammatory reaction. There is no way in which I can make that diagnosis on the evidence. There was no external sinus and no way of telling whether sulfur bodies were present or not. Actinomycosis of the bowel, or of the appendix, although uncommon, is not so rare that it must not always be considered, but I have to drop that out of serious consideration because of lack of evidence.

The ileocecal area is a common location for tuberculosis. One wonders whether this patient had tuberculosis—probably of the cecum or terminal ileum, which had been removed. Possibly, she even had involvement of the bowel in a more diffuse way, which would have accounted for the diarrhea for so many years. Certainly, tuberculosis of the bowel is not one of the more common lesions. I do not know whether or not she had pulmonary tuberculosis, but a great many patients have a localized type of lesion in that area that is independent of pulmonary tuberculosis. The presence of pulmonary tuberculosis might be evidence in support of that diagnosis, but its absence would not be strong evidence against it. Certainly, I cannot exclude it; on the other hand I cannot make the diagnosis.

The next condition that has to be given consideration is ulcerative colitis. It is difficult to make a diagnosis of ulcerative colitis on this patient. She had watery but never bloody diarrhea for many years; she had urgency, which is certainly commonly associated with ulcerative colitis. There was no sigmoidoscopic or barium-enema examination at the time of the first operation; on the other hand there was a barium-enema examination on admission. It is my opinion that, if this patient had had ulcerative colitis of long standing, by the time of admission there would have been some evidence of changes in the large bowel consistent with it and possibly some findings on sigmoidoscopic examination. Ulcerative colitis must be mentioned particularly because I cannot completely eliminate carcinoma. If I am willing to accept ulcerative colitis as a background for the present illness I must think seriously of a carcinoma of the transverse colon as partially responsible for the mass. Because I do not believe there is evidence enough to warrant the diagnosis of ulcerative colitis I am not willing to accept this mass as representing a carcinoma. For lack of positive evidence I am compelled to drop those diagnoses.

An inflammatory mass around a diverticulum, I think, is farfetched and not really worth mentioning. The original process might have been diverticulitis, but I doubt it, and I am particularly doubtful if the present condition could be explained on this basis.

That brings me down to regional enteritis. I am not able to make a positive diagnosis or to exclude it. Statistically, it is much more common than tuberculosis. Regional enteritis is a fascinating and extraordinary condition. This was too long a history of continuing symptoms for regional enteritis. I am not sure whether we have seen a patient with regional enteritis who continued to have symptoms over so long a time. Also, there was no evidence of regional enteritis that involved any other segment of the bowel unless that little area was not compression but an area of involvement of the bowel itself. Regional enteritis is probably the most common cause of internal fistulas or internal sinus tracts. Dr. Gibbons has not been able to say whether or not this patient had a fistulous opening, and I do not see how he possibly could. She certainly had a fistulous tract that extended outside the bowel lumen; you agree with that, do you not, Dr. Gibbons?

DR. GIBBONS: Yes.

DR. MCKITTRICK: Of course, regional enteritis is, I assume, the commonest cause of internal spontaneous fistulous opening or a sinus tract of that type. It is certainly a frequent cause of long-standing masses in the right lower quadrant. Many of the symptoms might well have been associated with a condition such as regional enteritis. I do not think that I can exclude regional enteritis because of the apparent localization of this process in a small segment of bowel, but I do think that is evidence against it.

I had hoped that Dr. Gibbons would pass on to me some clue that might ring a bell, but, though he has been very helpful, he has not rung the bell. It seems to me that the diagnosis lies between tuberculosis of the bowel and regional enteritis. There are points against both, and there are certainly points in favor of one over the other. Somehow, this long-standing story, the diarrhea and the absence of other evidence of a lesion within the bowel make me favor tuberculosis rather than regional enteritis in this particular case. I think, not having made up my mind ahead of time, that I have talked myself into calling this

tuberculosis, and my reasons are not very convincing, even to me.

DR. DANIEL S. ELLIS: You ought to ask Dr. Gibbons what he saw this morning.

DR. GIBBONS: I am afraid I do not know what was seen. I did not give the patient a fluoroscopic examination this morning.

DR. ELLIS: A good small-bowel study was done this morning.

CLINICAL DIAGNOSIS

?Carcinoma in abdomen.
?Mucocele in abdomen.

DR. LELAND S. MCKITTRICK'S DIAGNOSIS

Tuberculosis of bowel.

ANATOMICAL DIAGNOSIS

Regional enteritis.

PATHOLOGICAL DISCUSSION

DR. ROBERT H. FENNELL, JR.: This patient was operated on with a preoperative diagnosis of abdominal tumor, with a question of carcinoma and mucocele. At operation a mass was found in the right lower quadrant into which ran the terminal ileum and the transverse colon, and the mass was adherent to some of the adjacent organs—the gall bladder and the right tube—and was stuck posteriorly. The small bowel as it came into the mass was twisted, and this was believed to be a volvulus. The mass was resected, and an ileotransverse colectomy was done. On dissection a large mass, made up of inflammatory tissue with a great deal of fat and scar tissue, lay behind the ileum, which ran around the mass in a circumferential fashion. The small bowel, in cross section, was thickened and fibrotic, and scattered, superficial ulcerations were present. Microscopically the ulcers were covered with a thick layer of exudate and had abundant granulation tissue at their base. There was virtually no normal mucosa. The muscularis mucosae and the submucosa were greatly thickened, with dilated lymphatics and lymphoid follicles. An inflammatory exudate of lymphocytes, plasma cells and monocytes was in the submucosa, and the same inflammatory reaction was present to a lesser degree out in the muscle layer and serosa. No granulomas were found, but the appearance, both grossly and microscopically, was otherwise typical of regional enteritis. The lymph nodes were enlarged, but no granulomas were identified. The colon was perfectly normal grossly and microscopically.

DR. GIBBONS: Could you see the fistulous tract in the mass?

DR. FENNELL: There was a blind pouch in the end of the colon, and I should suppose that was what you were seeing.

CASE 40312

PRESENTATION OF CASE

A seventy-nine-year-old retired Portuguese Negro laborer was referred to the hospital because of low-back pain and dyspnea.

Seven months previously he began to tire easily and lost his appetite. He also noted the onset of dyspnea and a pulling sensation in the left anterior portion of the chest with moderate exertion. These symptoms were relieved with rest. He lost 50 pounds in weight over the next six months, his weight going from 220 pounds to 170 pounds. Six weeks before entry, while he was doing heavy work, an aching low-back pain suddenly developed. The pain started in the left flank and went across to the right, though it was always worse on the left. He thought that the pain was in his hip bones and spine but pointed to his flanks in demonstrating it. It was steady and relieved somewhat by change of position or rest, but always ultimately recurred regardless of position. He denied frequency, nocturia or change in color of the urine. He entered another hospital four weeks before admission and had a dorsal slit in the foreskin of the penis for phimosis because of alleged obstruction to the outflow of urine. There was no change in the pain, and dyspnea had increased, so that he could scarcely walk to the bathroom. He denied any ankle edema or orthopnea; he had never taken digitalis.

He had worked as a laborer all his life. Thirty years before entry he was told that he had an infection in the left kidney; cystoscopic study was carried out, but he had never passed stones and denied further urinary symptoms. At the age of eighteen he had epigastric discomfort, with burning relieved by soda and milk, and was said to have "ulcers." Although he had had heartburn after meals all his life he denied symptoms specifically referable to ulcers. For a month or two before admission he noted a dry mouth, with a metallic taste and loss of sense of smell and taste. He stated that he had pains in the abdomen "like a ball of fire" that were not affected by food intake. He denied melena and diarrhea but had slightly more constipation than before, now requiring cathartics. Hypertension was known to have been present for five years, with blood pressures "over 200." He was given pills at that time with no change in blood pressure and was placed on a diet. He limited salt to a certain extent. He had never had headaches, dizziness or episodes of unconsciousness.

Physical examination disclosed a well developed and well nourished man who appeared much younger than his stated age. The neck veins were flat, and the chest clear. The heart was enlarged, the border extending 2 cm. to the left of the midclavicular line in the fifth intercostal space. There was a Grade 2 apical systolic murmur, and the aortic second sound was louder than the pulmonic. The abdomen was obese, and the liver edge was felt 3 fingerbreadths below the

right costal margin. No other masses were palpable; peristalsis was normal, and there was no tenderness. There was granulation tissue about the healing incision of the foreskin. No edema or clubbing of the extremities was noted. The prostate was not enlarged.

The temperature was 99°F., the pulse 124, and the respirations 32. The blood pressure was 190 systolic, 100 diastolic.

Urinalysis showed a specific gravity of 1.006, a pH of 5.5, a + test for albumin and a + test for sugar; the sediment contained occasional hyaline casts, 0 to 1 white cell and many oxalate crystals per high-power field. The urine was negative for Bence–Jones protein. Examination of the blood revealed a hemoglobin of 14.5 gm. per 100 cc. and a white-cell count of 10,000, with 52 per cent neutrophils, 36 per cent lymphocytes, 6 per cent monocytes and 6 per cent eosinophils. The total protein was 7.4 gm., the albumin 4.4 gm., the globulin 3.0 gm., the nonprotein nitrogen 35 mg., the calcium 9.6 mg., the phosphorus 3.2 mg., the alkaline phosphatase 6.8 units, the acid phosphatase 1.4 units, the fasting blood sugar 184 mg., and the bilirubin 0.9 mg. per 100 cc. A bromsulfalein test demonstrated 49 per cent retention of the dye in forty-five minutes. The prothrombin time was 16 seconds (normal, 13 seconds), and cephalin flocculation was negative after forty-eight hours. The stools were guaiac negative on two occasions. An electrocardiogram disclosed sinus tachycardia, the only changes of note being low T waves in Leads 1, aVL and V_4, V_5 and V_6. A fasting gastric aspirate showed free acid. Sigmoidoscopic examination was negative to a distance of 18 cm.

Two upper gastrointestinal series were done within two days of each other. The first revealed a normal esophagus and a constantly deformed duodenal cap, with pooling of barium at the point of conversion of the folds. The duodenal loop and the portion of the small bowel visualized were not remarkable. The second examination was interpreted as showing marked antral spasm. The duodenal bulb never filled well, possibly because it was irritable but more probably because very little barium was left in the stomach; however, the duodenal bulb was deformed, and an ulcer crater was seen along the lesser curvature. A barium-enema examination was negative except for diverticula in the descending colon, and a film of the lateral lumbar region indicated only degenerative changes. A chest film showed the heart to be at the upper limits of normal, with slight congestion of the lung fields and a small pleural effusion on the right. In an intravenous pyelogram both kidneys were of normal size. The dye was excreted promptly from the right kidney and demonstrated a normal collecting system. No dye was seen at any time in the left kidney up to one hour. Films of the skull were normal. On the fourth hospital day a left retrograde pyelogram was done. The bladder and prostate were not remarkable. The left ureter was not dilated, and a catheter was passed nearly to the ureteropelvic junction. There was considerable hydronephrosis; the point of narrowing was seen to be at the ureteropelvic junction.

On the third hospital day the patient was noted to be still more dyspneic, without orthopnea or ankle edema. Pain deep in the left flank continued as before. He was digitalized and given mercurial diuretics, without significant effect. On the eighth hospital day the temperature rose to 102°F., and a urine culture grew out a few colonies of *Staphylococcus aureus* and *Staph. albus*. On the following day he was noted to have swelling of the right leg. The serum nonprotein nitrogen was 114 mg. per 100 cc., and the sodium 126 milliequiv., the carbon dioxide 21 milliequiv., the potassium 3.4 milliequiv., and the chloride 94 milliequiv. per liter. He was in severe respiratory distress, with crepitant rales halfway up the chest posteriorly, flat neck veins and cyanosis of the nail beds. He became weaker and died on the eleventh hospital day, despite symptomatic treatment.

Differential Diagnosis

Dr. Joseph C. Aub*: This is a fascinating case because as one reads the history the diagnosis appears obvious; later that diagnosis vanishes.

May I see the x-ray films?

Dr. Joseph Hanelin: The chest films are less impressive than the protocol implies. I trust this is the same patient. The heart is only slightly enlarged; there is little if any congestive change in the lung fields although hilar markings are somewhat prominent. I do not see any evidence of a pleural effusion. This is a matter of interpretation by the fluoroscopist, but in going over the spot films, we may be looking at old pleural thickening at the right base rather than free fluid.

Dr. Aub: Are you sure that these are the chest films? This man was so dyspneic that he could not even walk to the bathroom.

Dr. Hanelin: It has the same unit number; that is all I can say. I also wondered if this was the same patient.

Dr. Aub: You are making this much harder for me.

Dr. Hanelin: The evidence for congestion is at best questionable. The examination of the kidneys by intravenous pyelography showed a normal right kidney; the left kidney was not demonstrated until a retrograde study was done. This revealed a fairly severe hydronephrosis on the left, with obstruction apparently at the ureteropelvic junction. This type of obstruction is often associated with an aberrant vessel or a constrictive band in the area. I cannot demonstrate the actual cause of the obstruction.

Dr. Aub: Such a kidney ought to excrete dye.

Dr. Hanelin: Not necessarily.

The barium-enema examination is negative except

*Physician, Massachusetts General Hospital.

for the diverticula that were referred to in the protocol. The changes in the spine are striking and indicate a long life of fairly hard work. There is narrowing of all the intervertebral-disk spaces, with a great deal of spurring and sclerosis of the bodies. The bones are amazingly well mineralized for the patient's age—he was about eighty, I believe, but the bones appear to be those of a much younger person.

DR. AUB: I do not see the left kidney at all.

DR. HANELIN: The outline of the left kidney is obscured; it is not a huge kidney although it is probably somewhat enlarged. In the gastrointestinal examination the only important finding is the deformity of the duodenal bulb, which is fairly characteristic of that caused by an old ulcer. There is no obstruction. The skull films are normal except that there seems to be an abscess around one of the teeth.

DR. AUB: This man, who had been sick for seven months, lost a great deal of weight, had hypertension for many years, had diabetes and died in uremia. He was very short of breath on admission, and yet the laboratory data were normal except for the abnormal bromsulfalein retention and elevated alkaline phosphatase—evidence of some liver disease. I think I must say that he had diabetes, that he had a duodenal ulcer, that he died of uremia and that he had a hydronephrosis on the left. All those points are obvious.

Why was he short of breath for so long without evidence of great kidney insufficiency and an x-ray film of the chest that appeared normal? Did he have polyarteritis nodosa? The eosinophil count and blood pressure were high, but I do not think he had enough evidence for that disease. With a high blood pressure, although he may have had a chronic glomerulonephritis, I believe that at his age he had an arteriolar nephrosclerosis, which may have accounted for the loss of sodium terminally. No mention of the diabetes was made after admission; there was no evidence of diabetic acidosis.

Neither uremia nor acidosis is a good explanation for this man's severe illness of seven months' duration, with severe dyspnea and loss of weight, associated with a normal nonprotein nitrogen and quite normal blood findings; therefore, one has to think of some other condition in which the blood can be normal. The place to look for the solution of this problem is in the kidneys, particularly the left kidney. Was this lesion due to an aberrant vessel or to a neoplasm? This seven months of feeling "seedy," with tremendous dyspnea, means a neoplasm to me rather than a uremic condition primarily.

Where would the neoplasm have been? It may have involved the left kidney—a hypernephroma or adenocarcinoma. Frequently, metastases of such tumors to a lymph node occlude the ureteropelvic junction. Many of them metastasize to the lungs, and these metastases may not show in the x-ray films. Metastases to the liver, which are next in frequency, may account for the high alkaline phosphatase and the abnormal tests of liver function. Moreover, the liver was enlarged. Such tumors, even before they metastasize through the vein, may spread through the lymph nodes to the lung and the bone. I do not think such intense dyspnea for so long a time occurs with uremia, and this man obviously did not have cardiac disease; therefore, he must have had some condition that caused "stiff" lungs. If he had "stiff" lungs for seven months I think he had a lymphatic spread of a neoplasm to the lungs that made them "stiff." It is on that basis that I think he had a hypernephroma.

I have never seen "stiff" lungs from a hypernephroma. Hypernephromas, however, spread through the lymphatics to the lungs; I do not see why such metastatic spread could not have been present with normal x-ray films of the chest (as they may be when lymphatic spread of metastases from breast cancer are present). With all the accessory diagnoses that I have made, therefore, I am going to say hypernephroma with metastases.

DR. WALTER BAUER: Are not the findings more consistent with cancer of the pancreas, with marked lymphatic spread in the lungs? Such a finding can be very prominent in patients with carcinoma of the pancreas.

DR. AUB: The pain as described was not where pain from cancer of the pancreas occurs. The patient had diabetes. I think the diagnosis of carcinoma of the pancreas has a good possibility of being correct. The primary origin of widespread abdominal neoplasms is not easy to ascertain.

CLINICAL DIAGNOSES

Uremia.
?Carcinoma of pancreas, with metastases.
Hydronephrosis, left, with pyelonephritis.
Hypertensive heart disease.
Duodenal ulcer, active.

DR. JOSEPH C. AUB'S DIAGNOSES

Hypernephroma, with lymphatic spread to lungs.
Duodenal ulcer.
Diabetes.
Hydronephrosis, left.
Uremia.

ANATOMICAL DIAGNOSES

Colloid adenocarcinoma of pancreas, with extension to retroperitoneal tissues and metastases to stomach, spleen, liver, ileum, lumbar vertebras, adrenal gland, left ureter and lymphatics of lungs.
Thrombophlebitis of right common iliac, femoral and popliteal veins.
Multiple pulmonary emboli, old, small and recent.
Diverticulosis of small and large bowel.
Splenic infarct.
Cardiac hypertrophy.

Pathological Discussion

Dr. Edgar B. Taft: I was pleased to hear Dr. Aub come out so flat-footedly for carcinoma metastatic to the lungs because I remember a patient with clinical signs and symptoms not unlike those in the case under discussion on whom he made this diagnosis on the basis of similar dyspnea. That patient had carcinoma of the breast, and autopsy showed carcinomatosis of the lungs. As Dr. Aub said, the patient under discussion had so many diseases that it is difficult to know which anatomical findings to discuss first. I might start with the fact that there was thrombosis of the right common iliac, femoral and popliteal veins. Multiple emboli were found in the branches of the pulmonary artery. There were small emboli distally, which had perhaps been there for some time, and fairly good-sized emboli in the larger branches to the right and left lungs, which apparently had been present for a short time.

Dr. Aub: Was that the cause of death?

Dr. Taft: I wondered if the small emboli in the distal parts of the lung might not have increased the patient's dyspnea and perhaps have been a contributing factor in his death.

Dr. Aub: They could not have made him dyspneic for seven months.

Dr. Taft: Did he not have an exacerbation of the dyspnea some weeks before entry?

Dr. Bauer: He had one exacerbation in the hospital.

Dr. Taft: Microscopical examination of the lung showed small areas of infarction, which were not prominent and were not noticed on gross inspection.

The main disease was in the pancreas. There was a colloid adenocarcinoma of the body and tail of the pancreas of the sort that is thought to arise from ductile epithelium. It had completely replaced the body and tail, had extended widely through the retroperitoneal tissues on the left, had involved the surface of the stomach and the spleen, had destroyed the adrenal gland and had caused compression of the ureter on the left at the ureteropelvic junction, with the findings that were demonstrated in the x-ray films. There was considerable hydronephrosis of the left kidney, with severe chronic and acute pyelonephritis, and also a small perinephric abscess on the left. In addition there was a solitary metastasis, 2 cm. in diameter, in the right lobe of the liver that seemed hardly enough to have caused the abnormalities in bromsulfalein retention and alkaline phosphatase. There was also a solitary metastasis on the surface of the ileum not far from the ileocecal valve, and metastatic involvement of the fourth and fifth lumbar vertebras. On microscopical examination there was extensive lymphatic spread in the lungs that must have accounted for the seven months of dyspnea.

There were several other conditions, such as diverticula of the small and large bowel, that probably had little to do with the patient's death, as well as a small diverticulum of the first portion of the duodenum, which was thought to be a manifestation of an old ulcer. No typical ulcer was found, so we wondered if this produced the x-ray findings of ulcer. The heart was somewhat enlarged. There were small splenic infarcts that were probably related to the extensive carcinoma although the splenic artery was patent. The splenic vein was not identified in the mass of peripancreatic tumor.

Dr. Aub: Of course, venous thromboses occur with carcinoma of the pancreas. I still do not believe one is justified in making a diagnosis of carcinoma of the pancreas because of the thrombosis of the veins of the left leg, but the disease should have been mentioned.

Dr. Taft: Venous thromboses occur in 20 per cent of the patients with pancreatic carcinoma, I believe.

Dr. Farahe Maloof: What about the loss of smell and taste?

Dr. Taft: The brain was grossly normal; it has not yet been examined microscopically. There were no gross anatomic changes to account for such findings.

A Physician: Is there any known reason for the involvement of the veins in pancreatic disease?

Dr. Taft: I do not know that there is anything but the empiric clinical pathological observation; I do not know of any physiologic reason for this association.

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INCIDENCE AND PREVALENCE

THE prevailing use of the term "prevalence," in medicine as in ordinary parlance, is the one sanctioned by Webster; its biostatistical companion, "incidence," however, has a connotation so far removed from that defined by America's most persistent lexicographer that some attention to the matter is warranted—if for no other reason than to demonstrate that the second edition of the *New International Dictionary*, last printed as late as 1949, is already out of date.

Prevalence is reasonably defined as "the quality, condition or fact of being prevalent; now, usually frequent occurrence, general or widespread acceptance, usage, dissemination or the like; as, the prevalence of burglaries, of a fashion, of radios, or of a rumor." So far so good.

The difficulty arises when one contemplates the incidence as well as the prevalence of burglaries, radios or rumors. Here Mr. Webster is less serviceable to the aspiring statistician in that he considers incidence as an "Act, fact, or manner of falling upon or affecting; also range of occurrence or influence."

Supposing that the incidence of burglaries has risen like that of measles to a new high, how is the word "incidence" to be interpreted? The closest that Webster comes to satisfying precise standards is with the phrase "range of occurrence."

Since this journal, among others, seeks to guard and nourish the scientific niceties, it is high time to emphasize the definitions of these two words according to statistical usage. When used carelessly they may appear synonymous,—indeed the prevalence of disease, such as cancer, may at times be equal to its incidence, —but they are actually no more synonymous than "that" and "which," the employment of which (as well as of that) was established, although not irrevocably, some time ago.

The following definitions are therefore suggested as meeting ordinary scientific requirements:

> ***Prevalence***: **number of cases—that is, of affected persons—existing in a specified population at a particular moment; thus, the current prevalence of tuberculosis is commonly expressed as the number of all cases (old and new) existing at last count per 100,000 persons.**
>
> ***Incidence***: **the number of new cases or events occurring during a prescribed period in a specified population; thus, the incidence of tuberculosis expressed as a rate is the number of new cases recognized and reported per 100,000 population per year. For poliomyelitis weekly incidence is sought.**

The nub of the difference between prevalence and incidence is in the momentary quality of prevalence as contrasted to quality of duration implicit in incidence figures whether the stated intervals are weekly, monthly or annual. In brief, prevalence is a counting; incidence is a rate of occurrence. The difference is one of time, like that between snapshots and time exposures.

de VILLIERS FOUNDATION AWARD

THE *Journal*, two years ago, publicized the offer of a considerable prize to be awarded by the Robert Roesler de Villiers Foundation, Incorporated. This award was to be made for the most important paper submitted that contributed significantly "to the knowledge of the nature, causes, origin, treatment or cure of acute leukemia and allied diseases."

The winner of the first contest was announced last fall as Dr. Ludwik Gross, chief of research at the Veterans Administration Hospital, Bronx, New York; the prize was given for his work in support of the theory that leukemia of mice, at least, is caused by a filtrable virus. The award was made on October 20 at the New York Academy of Medicine with Dr. Maxwell M. Wintrobe and Dr. William B. Castle, members of the jury, participating, and a number of distinguished guests in attendance.

Since there is as yet no indication from what source the prevention, cure or control of leukemia will eventually come, attempts must be continued to stimulate thought and promote investigation in all quarters. The increased interest shown in the second contest of the Foundation is therefore encouraging. Whereas under "Contest I," of 1952, 30 papers were submitted, of which Dr. Gross's was the winning entry, under "Contest II," of 1953, 226 papers and suggestions in 6 different languages have been received from 22 countries. Considerable work in the tabulation, screening and translation of such a volume of material is obviously in order before the judges can even begin to select the winner of this second competition.

CIRCULATORY INCREASE

THE *Journal* plodded past some sort of milestone with its issue of July 15, when the paid circulation exceeded the 30,000 mark. Its subscribers, actually numbering 30,131 at that particular moment in the history of medicine, fell into certain natural categories—6522 Massachusetts Medical Society members, 17,605 "regulars," 5899 students and 105 New Hampshire Medical Society members who indulge in full subscriptions although at a special rate. An additional 530 members of the New Hampshire Medical Society receive the *Journal* once a month by special arrangement.

Although the *Journal* is now in its hundred and forty-second year of continuous publication, its circulatory increase has paralleled the country's changes in population only roughly if at all. Thus, in 1934, the peak circulation was approximately 6000, representing only a few subscribers more than the membership of the Society at that time. In 1944 this figure had grown to approximately 15,000, which, during the last troubled decade, has almost exactly doubled.

The *Journal* appreciates its good fortune in having apparently quickened the interest of this substantial number of physicians whose subscriptions, according to the records of the mailing department, draw it to practically every country in the world. This even includes the passage, by some sort of osmotic process, through the very Iron Curtain itself.

Dr. Bard, of Savannah, has used the mur. tinc. of iron in scarlet fever, with great success, in doses of from five to eight drops in mucilage every four hours.

Boston M. & S. J., *August 9, 1854*

MASSACHUSETTS MEDICAL SOCIETY

JOHN HOMANS

1877–1954

John Homans was among the most colorful and important medical figures of his time. Always on fire with enthusiasm, he found in each new experience an adventure to be relished and shared with his neighbor. This flame was as bright in 1954, when he invented and built a prefabricated dollhouse for his beloved grandchildren, as in 1895, when he "fought

like a wildcat" as center on his freshman football team. Whether it led to grafting fruit trees, hunting the New England grouse, playing tennis, squash or bridge or supporting the Boston Red Sox, it was a source of warmth and stimulation to all who drew near.

Adjectives are inadequate to describe him, and illustrative anecdotes are surely open to criticism from the hundreds of his friends who would think some other story more appropriate. By some he was termed a humorist, but his humor was not of the canned-story sort. It was a mischievous laughter at human foibles. If it was occasionally directed at personalities, the target was most often himself. He used to quote Dr. William Mayo's remark to him as he was leaving Rochester after a visit, "We dislike to see you leave, John; we were just getting used to you."

His associates loved him and chuckled with him. Affectionate nicknames were applied. His father had been called "Uncle John." The same name was given to the son by students who had never heard of the father. In this he took pride. Another, "Honest John," was particularly deserved because he was totally devoid of guile. Despite the unpredictability of his mercurial temperament it never engendered suspicion or fear among his associates. They knew where they stood — namely, on an equal basis with him in the business of working and living.

His personality was characterized by a combination of modesty (he did not wish his illuminating Gay Lecture on "The Care of the Patient" to be published) and the desire for recognition that certain spirits require as assurance that their efforts are effective. In this respect he was more interested in the reaction of his students than in the approbation of his contemporaries, whose disapproval he sometimes seemed to welcome. There was nothing that he loved better than a good professional squabble. But in the students his interest was serious and profound. The dedication to him of the *Aesculapiad* of the Class of 1934 was of deep importance in his life, and at one time he was disturbed because he had not been made president of the Boylston Society, an honor that came to him shortly thereafter.

He was a great friend. He had no illusions about his friends, for he had none about himself, but this quality of honesty in appraisal made him the more loyal. The obituary he wrote in 1941 on his close friend, Dr. E. A. Codman, is characteristic. Here is no eulogy. Eulogies are good to write since they act as an emotional cathartic for an overwrought author. But rarely are they useful to a reader who is looking for an analysis of a personality. Dr. Homans' lucid piece brought Dr. Codman, who above all people wanted the world to know him as he was, back among the living forever. Such is the nature of friendship.

As a teacher, Dr. Homans used the case method. He was an ideal bedside teacher: impatient with statistics, he preferred to gather a few patients around an idea. The human interest of those patients interpreted through the Homans personality constituted a memorable experience. His knowledge of the history and principles of a subject was profound, but his presentations had a quality far removed from dogma. Although no one more than he preached an awareness of the broad ignorance of practitioners of medicine and surgery, he was the opposite of an inactive therapist. His treatment was aggressive and rode on the wings of enthusiasm for a new or an old idea. The trait ran in the family. Dr. Homans liked the story of his father, who, when asked what he would do differently if he had his life to lead over again, answered, "Give larger doses of Dover's powders!"

His ability to continue to expand the horizons of his knowledge and his teaching ability after he had reached the "retiring" age was extraordinary. In the last year of his life he was intensely interested in the potentialities of reconstructive surgery for arteriosclerosis, and in a recent case correctly predicted that a patient would show by arteriography a lesion favorable for surgery when most of the younger men who had been growing up with the field had thought the opposite.

As an author he was a connoisseur of articulate expression. He was a "luminous writer" (an expression he himself used of Paget). He had a facility for injecting into his prose a cohesiveness that made it spring to life as a dynamic organism moving in rhythm. The historical prefaces to the chapters of his *Textbook* are classics:

> Woman has been subject to many crucial surgical experiments. The earliest trial battles with bacteria were fought in midwifery, and the first steps in abdominal surgery were taken in attempting to heal by operative means the great ovarian cysts, which for ages had carried endless disability and suffering. It is now almost impossible to imagine the number of invalids with swollen abdomens and drawn, pinched faces who were ready, when surgery could give even a fighting chance of relief, to offer themselves for a hazardous operation.

His medical pen was restless for half a century and provided over 100 items. His greatest love was the *Textbook of Surgery,* which went through six editions and occupies a unique position in all surgical literature so far as readability is concerned. In later years he frequently hoped that it would be taken up by a younger man and perpetuated. He was not to be consoled by the assurances of his friends that no one else was capable of doing so. But this was truly the case, and because of the book's inimitable personal quality, its impact as a memorial to its author in the annals of medical history will be the brighter for its having been preserved intact.

His professional articles were models of restraint with respect to imaginative license, although the case material was characteristically human. In his speeches and informal talks, however, one inevitably heard the music again: "Now pain in the left lower abdominal quadrant is, so far as I know, the most baffling symp-

tom known to surgery and occurs as a rule in females of almost unparalleled dreariness."

As an astute and beloved clinician he was second to none. It had been hard for him to wrench himself away from the tradition of his father and of Dr. Richardson and pursue a so-called academic life and thus limit his private practice. But lucky were the patients who penetrated to his consulting room. They loved him and followed him through his life. Though he was as blunt with them as with others, they, too, thrived upon it. His touch was that of a master. The following is his frank appraisal of one aspect of the doctor-patient relation:

> A "good" patient is one who has an interesting ailment capable of cure and at the same time continues to look pleasant, understands directions, asks very few questions and never complains. A "bad" patient begins by telling a poor story, full, not of fact, but of the alleged opinions of many physicians, is not easy of diagnosis and contrives to irritate and bewilder the attendants. Such a patient complains continually, asks questions innumerable, and whether things go well or ill, never gives the attendants the satisfaction of seeing her made happy. There are, of course, degrees of "badness." Some patients are "terrible" while others are just "difficult." The truth is that they are all "sick."

His contributions from the scientific and professional aspect were great. His interests were too broad for a specialty. He was the true general surgeon. His first report was written in 1905 in collaboration with his classmate, T. J. Burrage, on work done in Councilman's laboratory, which started when they were in medical school. The subject, prophetically, was the histology and pathology of the mitral and aortic valves. He later became a neurosurgeon under Cushing, and at the same time was interested in the Eck fistula for portal hypertension, one of the objects of his researches in the Hunterian Laboratory in Baltimore in 1908. He was the first in this country to attempt a portacaval shunt in man (1914). His work on the islands of Langerhans, first with Starling in London and later at the Peter Bent Brigham Hospital (1915), indicated an awareness of the nature of diabetes mellitus that was far ahead of anything before Banting and Best. From these signal contributions he went on to become one of the founders of the American school of vascular surgery. His influence in this area has been recognized by the establishment of the Homans Lecture in the Society for Vascular Surgery, he himself being the subject of the first lecture.*

He trained at Hopkinson's School in Boston and graduated from Harvard with the Class of 1899. He led his class in medical school, from which he graduated in 1903, and spent the next five years, first as intern at the Massachusetts General Hospital in surgery and then as assistant to Dr. Maurice Richardson, years which he later humorously and affectionately described in the *Harvard Medical Alumni Bulletin* (1950). Apparently, there had never been any question about his going into medicine. Three of the same name had preceded him in direct line. There had never been a thought by him or his parents that the "silver-spoon" heritage could exert an enervating effect. Once the forceful personality was recognized, such a possibility was out of the question. The heritage was of independence and service, qualities badly needed in all ages of medicine.

In 1908, at Dr. Richardson's suggestion, Homans went to Johns Hopkins to work for a year with Harvey Cushing in the Hunterian Laboratory. He then returned to the Massachusetts General Hospital as a junior member of the staff, with a particular interest in neurosurgery. In 1912 he was selected by Cushing to come with him to the new Peter Bent Brigham Hospital, before which he was to be sent abroad for study. He chose, with Dr. Cushing's aid no doubt, the laboratory of Professor Starling in London, where he labored with diligence. Much of his time off during that year was spent in attending the Gilbert and Sullivan operettas, most of which, as subsequent operating assistants of his can testify, he committed to memory. His friend, Dr. Francis Peabody, who was also in London at the time, was a stimulating companion. On his return here in June, 1913, he married and enjoyed thereafter a warm and rewarding family life.

In the years of World War I, before the participation of the United States, he worked at teaching and at productive research on the islands of Langerhans, leading to his most illustrious scientific paper, "A Study of Experimental Diabetes in the Canine and Its Relation to Human Diabetes" (*J. Med. Research* **33**:1, 1915). In 1917-1918 he served with an evacuation hospital in France, attaining the grade of major, and afterward returned to work at the Peter Bent Brigham, where, with a year's interlude in 1936-1937, when he became professor of surgery *pro tempore* at Yale, he remained until his death. His numerous honors and memberships in professional societies need not be detailed here. He was not, in any sense, a joiner. He contributed to organizations by being a member and felt little urge to be one of those who administer or determine policy. Nevertheless, he could not but naturally succeed to the top position in the New England Surgical Society, an organization standing for the things that were in his blood whose meetings he attended until his death.

We must say farewell to one whose like we cannot expect to see soon again, a rugged individualist too big for one school of surgery, occupying no "slot" in the sense that another can step up when he has stepped down, but one whose departure has already demonstrated how much he was needed. Let us pray that some mother's son now alive will grow to give future medical students an appreciation of the honor and fullness of a physician's life in the traditions established by this man.

R. W.

*Delivered by his affectionate and illustrious pupil, Dr. D. C. Elkin, of Atlanta, and published in the *New England Journal of Medicine* (**245**: 997, 1951).

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

DISCONTINUATION OF POLIO RÉSUMÉ

Since 1948 the Department of Public Health has issued annually, from July 1 to the end of the poliomyelitis season, a weekly report of the incidence of poliomyelitis in the Commonwealth. Copies have been sent to public-health personnel, to the hospitals of the State and to interested physicians.

The primary purpose of the résumé was to notify various agencies of the danger period in scheduling of elective tonsillectomies and other throat operations. This was thought to be essential because the medical literature indicated that poliomyelitis contracted shortly after such an operation was likely to be bulbar in type; the mortality in bulbar cases is quite high, of course.

Some years ago articles began to appear that questioned the importance of the interval between an operation and the development of bulbar poliomyelitis.

In 1952 Top[1] analyzed the figures compiled over several years at the Herman Kiefer Hospital in Detroit. He showed that the interval between the throat operation and the onset of poliomyelitis was of little significance. A person whose tonsils and adenoids had been removed three months, three years or thirty years before was just as likely to have the bulbar type as one whose operation had been done during the previous three weeks.

In 1954 Weinstein and his co-workers[2] presented a similar study of the cases at the Haynes Memorial Hospital in Boston. Their analysis confirmed the conclusions of Top and the previous writers on the subject.

The important point to remember is that the lack of tonsils and adenoids increases the risk of the bulbar type on contraction of poliomyelitis. Anderson and Rondeau[3] estimate that four times as many cases of bulbar poliomyelitis occur among those whose tonsils and adenoids have been removed as among those who still retain them.

Since the time element is of little medical importance, there is no reason for the Department to continue the résumé, whose primary function was to recommend the suspension of throat operations.

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USE OF ANTIBIOTICS IN SYMPTOMLESS CARRIERS OF ENTERIC ORGANISMS

THE current increased incidence of enteric disease has emphasized the frequent finding of salmonella or shigella in the stools of completely asymptomatic subjects. Such persons are usually transient carriers, whose stools generally become negative without any special treatment.

The use of antibiotics in the absence of clinical symptoms is decidedly questionable because their action in clearing up the stools is quite unreliable, and, by suppressing the normal intestinal bacteria, they may cause cases of severe and even fatal enteritis of staphylococcal or other origin. In view of the complications that can arise it seems wise to be extremely cautious in the use of antibiotics to eliminate salmonella or dysentery bacilli from stools of persons who have not been clinically ill at all or are clinically recovered. This statement is intended to apply to the asymptomatic patient, and is not to be construed as an argument against the judicious use of antibiotics while the patient is having actual symptoms of diarrhea.

The physician may encounter impatience on the part of the patient or family when stools remain positive longer than usual after discharge. The problem is particularly trying in small infants, who usually harbor the organisms longer than adults. In such cases it should be emphasized that the stools almost always become negative fairly soon without any special treatment. In the meantime reasonable precautions consist of care in washing of the hands after visiting the toilet and avoidance of the handling of any food consumed by others. With the exception of a food handler the person involved may ordinarily carry on his usual daily activities.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JUNE, 1954

RÉSUMÉ

DISEASE	JUNE 1954	JUNE 1953	SEVEN-YEAR MEDIAN
Chancroid	1	1	4
Chicken pox	1264	1410	1512
Diphtheria	1	3	12
Dog bite	2044	1426	1594
Dysentery, bacillary	15	14	5
Encephalitis, infectious	6	3	4
German measles	1203	821	437
Gonorrhea	178	177	222
Granuloma inguinale	0	1	0
Hepatitis, infectious	91	70	5†
Lymphogranuloma venereum	0	1	1
Malaria	1	1	1
Measles	4906	351	2556
Meningitis, meningococcal	6	9	6
Meningitis, Pfeiffer bacillus	1	3	5
Meningitis, pneumococcal	6	1	3
Meningitis, streptococcal	0	1	0
Meningitis, staphylococcal	0	0	0
Meningitis, undetermined	9	4	3
Mumps	2177	1637	1004
Poliomyelitis	10	6	5
Salmonellosis	20	6	7
Scarlet fever	364*	268	292
Syphilis	224	154	176
Trichinosis	4	9	2
Tuberculosis, pulmonary	192	177	188
Tuberculosis, other forms	11	9	13
Typhoid fever	3	5	2
Undulant fever	2	4	2
Whooping cough	141	150	150

*Includes streptococcal sore throat.

†Five-year median.

COMMENT

Diseases below the seven-year median were chicken pox, diphtheria and whooping cough.

Chicken pox was at the lowest level since 1940. Diphtheria has been lower only once in the past. This is the first time in over a year that whooping cough dropped below the number of cases reported in the same month during the previous year.

The diseases above the seven-year median were bacillary dysentery, German measles, infectious hepatitis, measles, mumps, poliomyelitis, salmonellosis and scarlet fever.

After a very low incidence in 1953 and early 1954 measles rose rapidly, and in June reached the highest figure since 1948.

Mumps, which has been on the upward trend since September, 1953, in June reached the highest level for the month since reporting began.

Salmonellosis continues to be discovered with great regularity. The high figure is due in part to food-borne outbreaks.

Geographical Distribution of Certain Diseases

The following diseases were reported from the communities named:

Diphtheria: Milford, 1.

Dysentery, amebic: Boston, 1.

Dysentery, bacillary: Boston, 7; Brockton, 1; Lawrence, 1; Southbridge, 1; Waltham, 2; Weymouth, 1; Worcester, 1; Wrentham, 1; total, 15.

Encephalitis, infectious: Fall River, 1; Lynn, 1; Springfield, 1; Waltham, 1; West Boylston, 1; Winthrop, 1; total, 6.

Hepatitis, infectious: Boston, 9; Bridgewater, 1; Brockton, 4; Brookline, 1; Cambridge, 11; Chelsea Naval Hospital, 3; Danvers, 1; East Longmeadow, 1; Fall River, 5; Fort Devens, 1; Hanover, 1; Kingston, 1; Lowell, 4; Lynn, 5; Oxford, 1; Peabody, 1; Plymouth, 2; Quincy, 3; Rutland, 1; Somerset, 1; Somerville, 2; Spencer, 2; Springfield, 5; Taunton, 2; Webster, 1; Wellesley, 1; Westfield, 1; Weston, 1; Westover Field, 4; Williamstown, 1; Worcester, 9; Wrentham, 5; total, 91.

Malaria: Waltham, 1.

Meningitis, meningococcal: Boston, 2; Brockton, 1; Danvers, 1; Malden, 1; Westover Field, 1; total 6.

Meningitis, Pfeiffer bacillus: Clarksburg, 1.

Meningitis, pneumococcal: Hampden, 1; Holyoke, 1; Medford, 1; Millbury, 1; Revere, 1; South Hadley, 1; total, 6.

Meningitis, mumps: Waltham, 1.

Meningitis, undetermined: Barnstable, 1; Boston, 5; Cambridge, 1; Southbridge, 1; Waltham, 1; total, 9.

Poliomyelitis: Falmouth, 1; Haverhill, 1; Marion, 1; Melrose, 1; New Bedford, 1; Newburyport, 1; Seekonk, 1; Wilmington, 1; Worcester, 1; Yarmouth, 1; total, 10.

Psittacosis: Belmont, 1; Boston, 1; Lexington, 1; Wellesley, 1; total, 4.

Salmonellosis: Boston, 3; Brookline, 1; Cambridge, 1; Framingham, 3; Hopkinton, 1; Marblehead, 1; Newbury, 1; Princeton, 1; Quincy, 1; Randolph, 1; Revere, 1; Salem, 1; Shrewsbury, 1; Somerville, 1; Southbridge, 1; Swampscott, 1; total, 20.

Tetanus: Rockland, 1; Worcester, 1; total, 2.

Trichinosis: Bellingham, 3; North Andover, 1; total, 4.

Typhoid fever: Cambridge, 2; Wellesley, 1; total, 3.

Undulant fever: Barnstable, 1; Becket, 1; total, 2.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Studies from The Rockefeller Institute for Medical Research: Reprints. Volume 147. 4°, paper, 616 pp. New York: Rockefeller Institute for Medical Research, 1953.

Orthopädische Konstruktionen. Arbeiten aus der Orthop. Univ. Poliklinik München, dem Fürsorgelazarett München, der Orthop. Univ. Klinik Leipzig, der Orthop. Klinik Sanderbusch/Oldenburg, 1912-1953. By Prof. Dr. Franz Schede. 8°, paper, 98 pp., with 141 illustrations. Stuttgart: Georg Thieme, 1953. DM 8.—(*Arbeit und Gesundheit*, New Series No. 52.)

Professor Schede deals with the apparatus used in the treatment of orthopedic conditions in persons of all ages. There are chapters on contractures in general and on the foot, upper and lower extremities, spine, congenital hip dislocation, spinal paralysis in children and artificial limbs. There is a bibliography of 50 references. This second edition has been revised and brought up to date.

Arzt und Neurose. By Professor J. H. Schultz. Second edition, revised. 8°, paper, 107 pp. Stuttgart: Georg Thieme, 1953. DM 8.40. (Distributed by Grune and Stratton, New York.)

The first edition of this small book was published in 1936. The author has revised his text and brought it up to date in this second edition. Neurosis is discussed, with special reference to psychotherapy in general practice.

Das Analzäpfchen in der Geschichte der Therapie. By Prof. Dr. P. Diepgen. 8°, paper, 44 pp., with 3 illustrations. Stuttgart: Georg Thieme, 1953. DM 4.20. (Distributed by Grune and Stratton, New York.)

Professor Diepgen presents the history of suppositories from the time of the earliest civilizations to the present. There is a bibliography with notes of 157 items. The monograph is suitable for medical-history collections.

Administrative Medicine: Transactions of the First Conference, March 9, 10, and 11, 1953, New York, New York. Edited by George S. Stevenson, M.D., medical director, National Association for Mental Health, New York. 8°, cloth, 176 pp. New York: Josiah Macy, Jr., Foundation, 1953. $3.00. (*Josiah Macy, Jr., Foundation Conference Transactions.*)

This new conference, sponsored by the Josiah Macy, Jr., Foundation, was a panel discussion of the various problems of mental and physical health confronting administrators of institutions and similar organizations. The 19 discussers are eminent in their particular fields. The volume should be in all medical libraries and available to all medical administrators.

Diagnosis of Acute Abdominal Pain. By William Requarth, M.D., clinical assistant professor of surgery, University of Illinois College of Medicine. With a foreword by Warren H. Cole, M. D. 8°, cloth, 243 pp., with 79 illustrations. Chicago: Year Book Publishers, Incorporated, 1953. $5.00.

The author discusses the diagnosis of acute surgical lesions within the abdomen. The first chapters, which deal with examination and differential diagnosis, are followed by a discussion of acute intestinal obstruction, traumatic wounds, indications and contraindications for operation, diagnosis in infants and the differential diagnosis of acute gastroesophageal hemorrhage. Lists of references are appended to the chapters; there is a good index, and the monograph is well published.

Pharmacology and Therapeutics: A textbook for students and practitioners of medicine. By Arthur Grollman, Ph.D., M.D., lecturer in pharmacology and toxicology, the Medical Branch, professor of experimental medicine and chairman, Department of Experimental Medicine, Southwestern Medical School, University of Texas, attending physician, Parkland Hospital, consultant in internal medicine, Baylor University Hospital, and consultant, Veterans Administration Hospital, Dallas, Texas. Second edition, revised and enlarged. 8°, cloth, 866 pp., with 127 illustrations. Philadelphia: Lea and Febiger, 1954. $10.00.

The first edition of this book, which was published in 1951, was reprinted three times. This second edition has been thoroughly revised, and many parts have been rewritten. The material is systematically arranged according to classes of drugs and therapeutic agents. The appendixes

deal with prescription writing and a classification of drugs according to their therapeutic uses. Lists of references are appended to the chapters, and there is a comprehensive index.

The Year Book of Drug Therapy (1953-54 Year Book Series). Edited by Harry Beckman, M.D., director, Department of Pharmacology, Marquette University Schools of Medicine and Dentistry, and consulting physician, Milwaukee County General and Columbia hospitals, Milwaukee, Wisconsin. 12°, cloth, 538 pp., with 73 illustrations. Chicago: Year Book Publishers, Incorporated, 1954. $6.00.

In this new volume in an important series abstracts of the worthwhile articles published between August, 1952, and August, 1953 are given. Considerable space is given to antibiotics and cardiovascular diseases. There are indexes of authors and subjects.

The Collected Papers of Otto Fenichel: First series. 8°, cloth, 408 pp. New York: W. W. Norton and Company, Incorporated, 1953. $6.50.

Dr. Fenichel was active in the field of psychoanalysis for over twenty-five years before his death in 1946. He was the author of a well known book, *The Psychoanalytic Theory of Neurosis,* and numerous papers. This volume contains a selection of articles in English; a second series will follow soon. The publishing is excellent, and the book should be in all collections on the subject.

Autopsy Diagnosis of Congenitally Malformed Hearts. By Maurice Lev, M.D., pathologist and chief of research laboratories, Mount Sinai Hospital of Miami, Miami Beach, Florida, and associate professor of pathology, University of Miami School of Medicine. 8°, cloth, 194 pp., with 115 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $7.50.

The author presents his subject in three parts: dissection and examination; individual abnormalities; and pathologic complexes. There is a bibliography of 22 pages and a combined author and subject index. The illustrations are excellent. The book should be in all collections on cardiology.

The Pathology of Trauma. By Alan R. Moritz, M.D., professor of pathology and director, Institute of Pathology, Western Reserve University School of Medicine, Cleveland, Ohio. Second edition. 8°, cloth, 414 pp., with 126 illustrations. Philadelphia: Lea and Febiger, 1954. $8.50.

Dr. Moritz has revised his book to bring it up to date. Much material dealing with the military aspects of medicine has been added to the text. The sections most drastically revised include injuries by gunfire, those incident to explosions, trauma and infection, and injuries of the organs of respiration and of the central nervous system. Extensive bibliographies are appended to the chapters. The book is well published and is recommended for all collections on trauma and legal medicine.

The Year Book of Radiology (1953-1954 Year Book Series). Radiologic Diagnosis. Edited by John F. Holt, M.D., associate professor, Department of Roentgenology, University of Michigan Medical School; and Fred J. Hodges, M.D., professor of roentgenology and chairman, Department of Roentgenology, University of Michigan Medical School. *Radiation Therapy.* Edited by Harold W. Jacox, M.D., professor of radiology, Columbia University College of Physicians and Surgeons, and chief, Radiation Therapy Division, Radiologic Service, Presbyterian Hospital, New York City; and Vincent P. Collins, M.D., professor of radiology and chairman, Department of Radiology, Baylor University College of Medicine, and radiologist-in-chief, Jefferson Davis Hospital, Houston, Texas. 8°, cloth, 462 pp., with 399 illustrations. Chicago: Year Book Publishers, Incorporated, 1953. $8.00.

This twenty-second volume in the series on radiology maintains the standard of excellence. A large number of articles have been abstracted to bring out the important points. There are indexes of authors and subjects, and the publishing is excellent.

Chronic Iliac Pain in Women. By H. B. Atlee, M.D., F.R.C.S. Ed. & Can., F.I.C.S., head, Department of Obstetrics and Gynecology, Dalhousie University, Halifax, Nova Scotia, Canada. 8°, paper, 65 pp., with 6 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $2.50. (Publication No. 198, *American Lecture Series.*)

The author describes 9 various conditions that may cause chronic iliac pain in women. The monograph is practical and sensible and should prove of value to the gynecologist and internist.

Frontal Lobes and Schizophrenia. Second Lobotomy Project of Boston Psychopathic Hospital. Edited by Milton Greenblatt, M.D., asistant clinical professor of psychiatry, Harvard Medical School, and chief of laboratories and research, Boston Psychopathic Hospital; and Harry C. Solomon, M.D., professor of psychiatry, Harvard Medical School, and medical director, Boston Psychopathic Hospital. 8°, cloth, 425 pp., with 41 tables and 34 illustrations. New York: Springer Publishing Company, Incorporated, 1953. $12.50.

This volume deals with the second lobotomy project of the Boston Psychopathic Hospital. The first lobotomy at the hospital was done in 1943, and studies made from 1943 to 1949 comprised the first project, described in 1950.

The material is divided into three parts: plan, methods, procedures and preoperative studies; effects of surgery of the frontal lobe—psychiatric, psychologic, sociologic, sociometric, physiologic and pathologic; and further elaboration of data. Lists of references are appended to the chapters, and there is a good index. The volume should be in all collections on the subject.

Infrared Absorption Spectra of Steroids: An atlas. By Konrad Dobriner, E. R. Katzenellenbogen and R. Norman Jones, Sloan-Kettering Institute for Cancer Research and the National Research Council of Canada. With a preface by C. P. Rhoads. 8°, cloth, 353 pp., with 308 illustrations. New York: Interscience Publishers, Incorporated, 1953. $11.50.

This atlas of spectroscopic curves has been published especially for chemists and endocrinologists who have been handicapped by a lack of data of this type. There is a bibliography of 48 titles and numerical and alphabetical indexes of the charts.

Dizziness: An evaluation and classification. By David D. DeWeese, M.D., clinical professor of otolaryngology, University of Oregon Medical School, head, Department of Otolaryngology, Portland Clinic, Portland, Oregon, chairman for instruction in otolaryngology, Pacific Coast Oto-Ophthalmological Society, and otolaryngologist, St. Vincent's Hospital, Doernbecher Memorial Hospital for Children and Multnomah County Hospital, Portland, Oregon. 8°, cloth, 80 pp., with 2 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $2.75. (Publication No. 176, *American Lecture Series.*)

This monograph was submitted by the author in 1949 as a candidate's thesis for membership in the American Laryngological, Rhinological and Otological Society. It discusses the two forms of vertigo, nonsystematized and systematized. Seventeen case histories are presented, and there is a short bibliography and an index.

Surgical Pathology. By Peter A. Herbut, M.D., professor of pathology, Jefferson Medical College, and director of clinical laboratories, Jefferson Medical College Hospital, Philadelphia, Pennsylvania. Second edition. 8°, cloth, 893 pp., with 528 illustrations. Philadelphia: Lea and Febiger, 1954. $14.00.

This second edition has been revised and brought up to date by the addition of 183 pages of new material. Chapters have been added on the adrenal glands and the central nervous system. Several chapters have been rewritten, including those on wound repair, thrombosis, burns, sacrococcygeal teratoma, mitral stenosis, histoplasmosis of the larynx and lungs, tricuspid atresia and subdiaphragmatic abscess. The illustrations have been revised, and 124 new ones have been incorporated. Lists of references are appended to the chapters; there is a good index, and the publishing is excellent.

NONCLINICAL NOTES

OFFICERS OF THE NEW ENGLAND ROENTGEN RAY SOCIETY

The following officers of the New England Roentgen Ray Society were recently elected: president, Dr. Jack Spencer, Portland, Maine; vice-president, Dr. Felix G. Fleischner, Boston, Massachusetts; secretary, Dr. Stanley M. Wyman, Boston, Massachusetts; and treasurer, Dr. Magnus I. Smedal, Boston, Massachusetts.

TUFTS COLLEGE MEDICAL SCHOOL APPOINTMENT

Dr. George W. Mitchell, Jr., of Wellesley Hills, has been appointed professor of gynecology and chairman, Department of Obstetrics and Gynecology, Tufts College Medical School.

NOTICES

FELLOWSHIP IN PROCTOLOGY

The International Academy of Proctology announces the establishment of a teaching and research fellowship in proctology under the direction of Dr. Marcus D. Kogel, of the Albert Einstein College of Medicine, New York City. The Academy has voted an annual grant of $1000 for three years for research and educational projects in proctology. The Academy also offers a free teaching seminar, open to all physicians, each year.

ARTHRITIS AND RHEUMATISM FOUNDATION FELLOWSHIPS

The Arthritis and Rheumatism Foundation announces a basic research fellowship program as follows: predoctoral fellowships ranging from $1500 to $3000 per year, for one year with prospect of renewal; postdoctoral fellowships ranging from $4000 to $6000 per year tenable for one year with prospect of renewal; and senior fellowships of $6000 to $7500 per year tenable for five years. Applications must be received before October 15. Forms may be obtained from the Medical Director, Arthritis and Rheumatism Foundation, 23 West 45th Street, New York 36, New York.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

Applications for certification for the 1955 Part I examinations of the American Board of Obstetrics and Gynecology should be submitted in July or August. All candidates for the examinations must submit with the application a plain, typewritten list of all patients admitted to the hospitals where they practice during the year preceding application, or request for reopening of application, with the diagnosis, pathological diagnosis, nature of treatment and end result.

Candidates for Part I examination must submit 20 case abstracts, of which 5 may be from residency service. Applications for examination or re-examination, as well as requests for resubmission of case abstracts, must be made before October 1 to the secretary, Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6, Ohio.

AMERICAN CONGRESS OF PHYSICAL MEDICINE AND REHABILITATION

The thirty-second annual scientific and clinical session of the American Congress of Physical Medicine and Rehabilitation will be held at the Hotel Statler, Washington, D. C., September 6 through 11. All sessions will be open to members of the medical profession. Instruction seminars will be open to physicians and therapists registered with the American Registry of Physical Therapists or the American Occupational Therapy Association. Further information may be obtained from the American Congress of Physical Medicine and Rehabilitation, 30 North Michigan Avenue, Chicago 2, Illinois.

COURSE IN LABORATORY DIAGNOSIS OF TUBERCULOSIS

A course in the laboratory diagnosis of tuberculosis will be offered by the Communicable Disease Center and the Division of Special Health Services, Public Health Service, at Chamblee, Georgia, November 15 through 26, 1954.

The course is open to all employed laboratory personnel who are approved by their state health officers. Laboratory directors and senior staff members may also apply. There are no tuition or laboratory fees. Reservations must be made well in advance. Application forms may be obtained from the Laboratory Training Services, Communicable Disease Center, Public Health Service, P.O. Box 185, Chamblee, Georgia.

AMERICAN MEDICAL WRITERS' ASSOCIATION AND MISSISSIPPI VALLEY MEDICAL SOCIETY

The eleventh annual meeting of the American Medical Writers' Association will be held at the New Hotel Sherman, Chicago, on September 24. The moderators will be Drs. Richard M. Hewitt, Mayo Clinic, and Clayton G. Loosli, University of Chicago.

The nineteenth annual meeting of the Mississippi Valley Medical Society will be held at the same place September 22 through 24. Further information may be obtained from Dr. Harold Swanberg, Secretary, W.C.U. Building, Quincy, Illinois.

SOCIETY MEETINGS AND CONFERENCES

AUGUST 13-23. Consultation Clinics for Crippled Children in Massachusetts. Page 1054, issue of June 17.
AUGUST 17-20. Argentine Congress of Thoracic Surgery. Page 708, issue of April 22.
SEPTEMBER 6-10. International Poliomyelitis Congress. Page 399, issue of March 4.
SEPTEMBER 6-11. University of Illinois College of Medicine. Annual Assembly in Otolaryngology. Page 1092, issue of June 24.
SEPTEMBER 6-11. American Congress of Physical Medicine and Rehabilitation. Notice above.
SEPTEMBER 7-10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.
SEPTEMBER 12-15. Second International Congress of Cardiology. Washington, D. C.
SEPTEMBER 13-15. American Association of Blood Banks. Page 968, issue of June 3.
SEPTEMBER 16-18. American Heart Association. Annual Scientific Sessions. Washington, D. C.
SEPTEMBER 22. New England Pediatric Society. Page 968, issue of June 3.
SEPTEMBER 22-24. Mississippi Valley Medical Society. Notice above.
SEPTEMBER 24. American Medical Writers' Association. Notice above.
OCTOBER 1 and DECEMBER 3, 1954; FEBRUARY 4 and APRIL 1, 1955. New England Society of Anesthesiologists. Page 1054, issue of June 17.
OCTOBER 7 and 8. Pan-Pacific Surgical Association. Page 1092, issue of June 24.
OCTOBER 8 and 9. Academy of Psychosomatic Medicine. Page 748, issue of April 29.
OCTOBER 11-15. American College of Physicians Course. Page 44, issue of July 1.
OCTOBER 16-22. American Occupational Therapy Association. Page 1092, issue of June 24.
OCTOBER 18-29. New York Academy of Medicine Graduate Fortnight. Page 44, issue of July 1.
OCTOBER 25-27. New England Postgraduate Assembly. Hotel Statler, Boston.
OCTOBER 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.
OCTOBER 27-29. International Symposium on the Hypophyseal Growth Hormone. Page 1092, issue of June 24.
OCTOBER 31–NOVEMBER 4. American Institute of Dental Medicine. Page 968, issue of June 3.
NOVEMBER, 1954-MAY, 1955. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.
NOVEMBER 3-5. National Society for Crippled Children and Adults. Page 44, issue of July 1.
NOVEMBER 12 and 13. Inter-Society Cytology Council. Page 968, issue of June 3.
NOVEMBER 15-26. Laboratory Diagnosis of Tuberculosis. (Course.) Notice above.
DECEMBER 5. American Academy of Dental Medicine. Page 1092, issue of June 24.
DECEMBER 8. New England Pediatric Society. Page 968, issue of June 3.
DECEMBER 13-17. Congress of Obstetrics and Gynecology. Page 748, issue of April 29.
JUNE 21-25, 1955. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

(Notices concluded on page xix)

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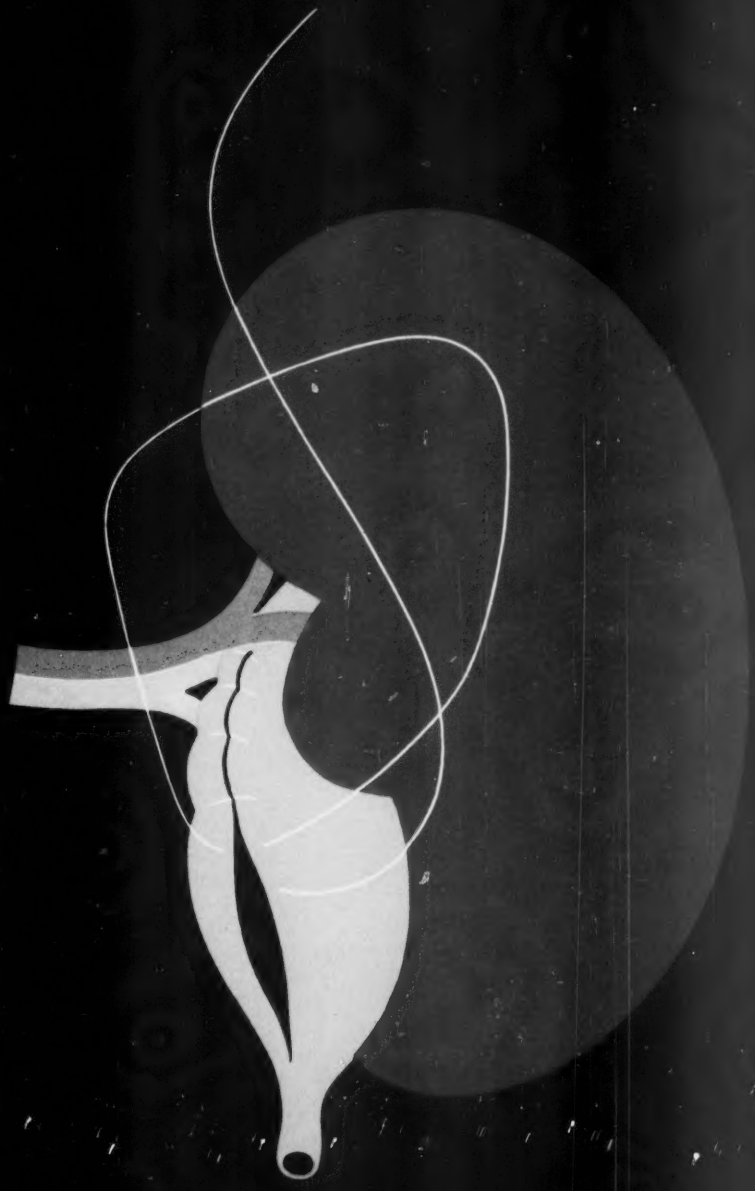
1. Grayzel, H. G., Heimer, C. B., and Grayzel, R. W.: New York St. J. M. 53:2233, 1953.
2. Heimer, C. B., Grayzel, H. G., and Kramer, B.: Archives of Pediatrics 68:382, 1951.
3. Behrman, H. T., Combes, F. C., Bobroff, A., and Leviticus, R.: Ind. Med. & Surgergy. 18:512, 1949.
4. Turell, R.: New York St. J. M. 50:2282, 1950.



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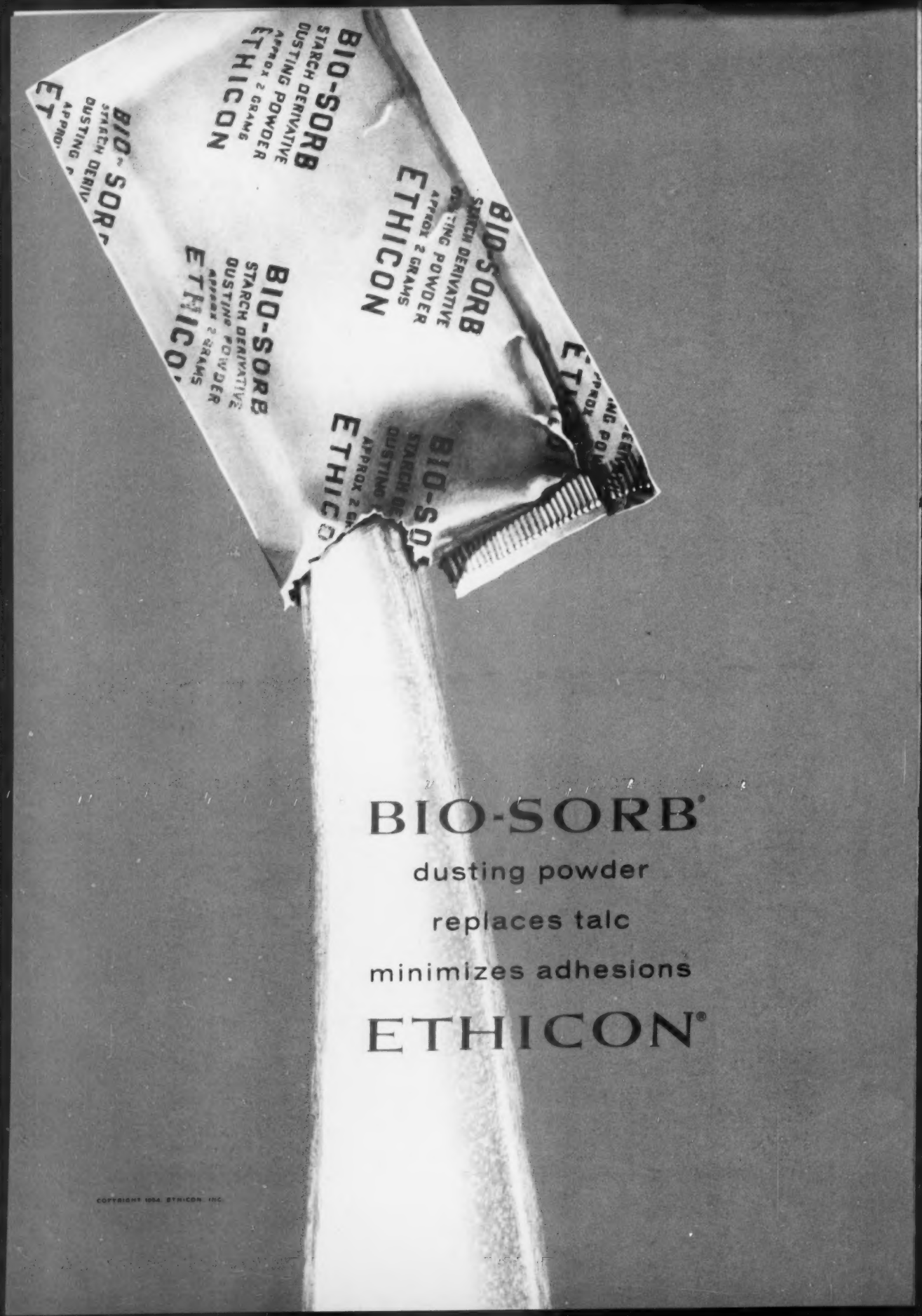

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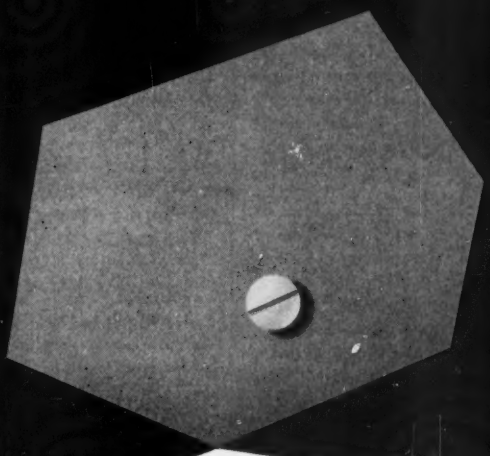

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CIBA
Summit, N. J.

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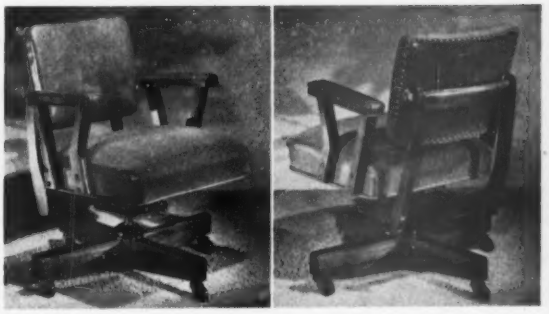

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NOTICES *(Concluded from page 246)*

CALENDAR FOR THE WEEK BEGINNING THURSDAY, AUGUST 12

THURSDAY, AUGUST 12
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*11:00 a.m. Thoracic Conference. Case Presentations of Unusual Heart Surgical Problems. Dr. Dwight Harken. Main Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Case Presentations and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.

FRIDAY, AUGUST 13
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, AUGUST 14
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

MONDAY, AUGUST 16
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Foot Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

TUESDAY, AUGUST 17
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

WEDNESDAY, AUGUST 18
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. Out-Patient Department.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

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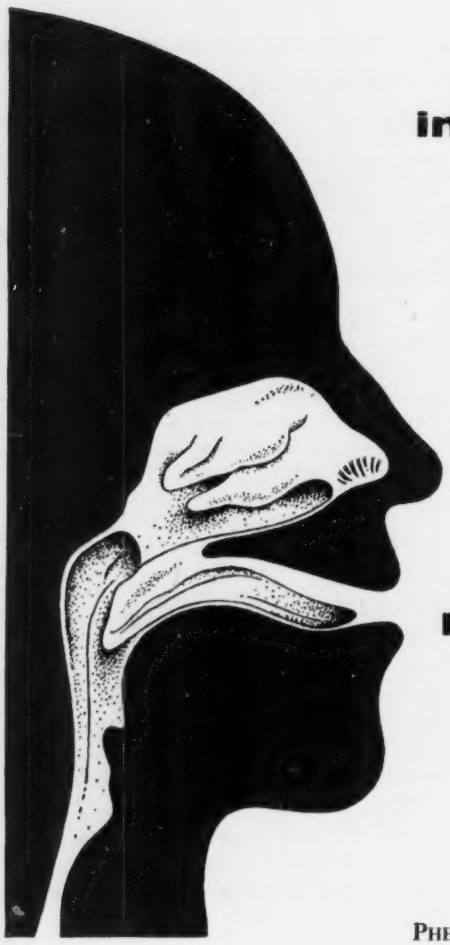

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1. Silbert, N.E.: Ann. Allergy *10*:328 (May-June) 1952
2. Peshkin, M.M., and others: Ann. Allergy 9:727 (Nov.-Dec.) 1951

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